# Amino acid metabolism

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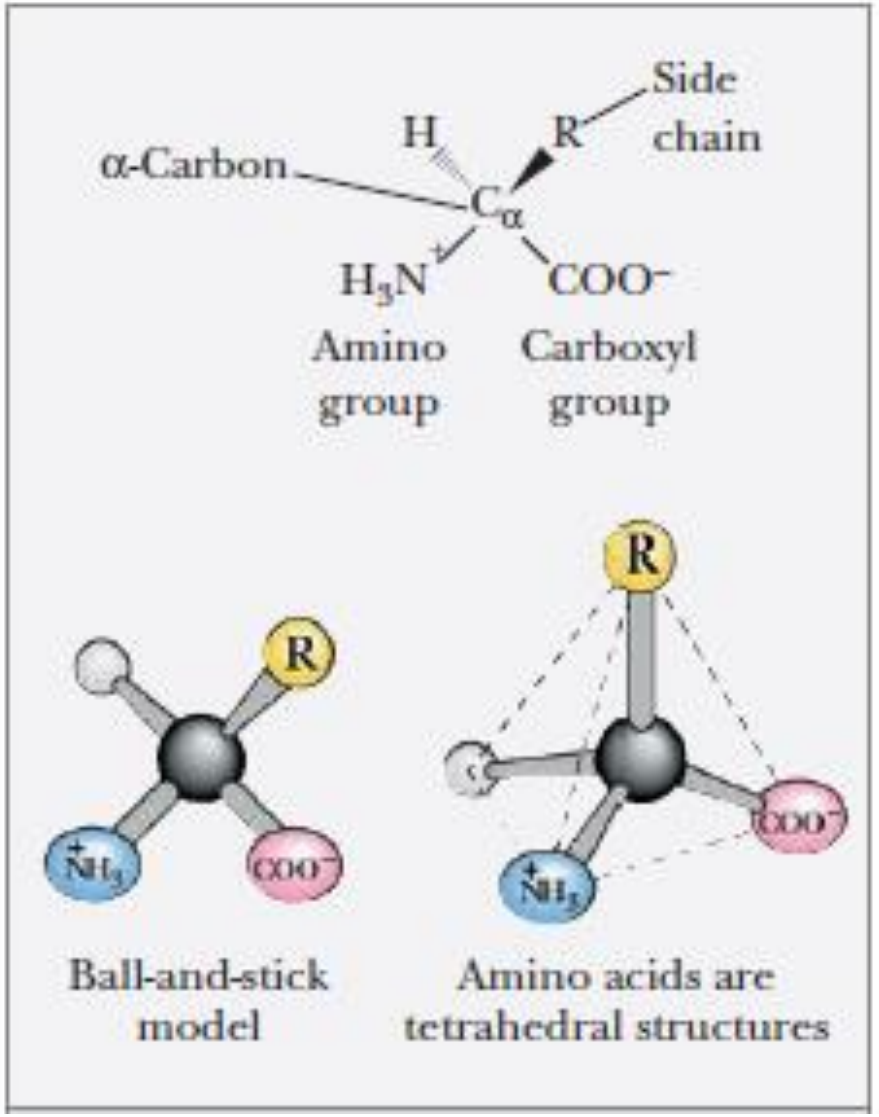
Biochemistry for Lippincott. Chapters 19-21

All images were taken from  Lippincott's Biochemistry textbook except where noted

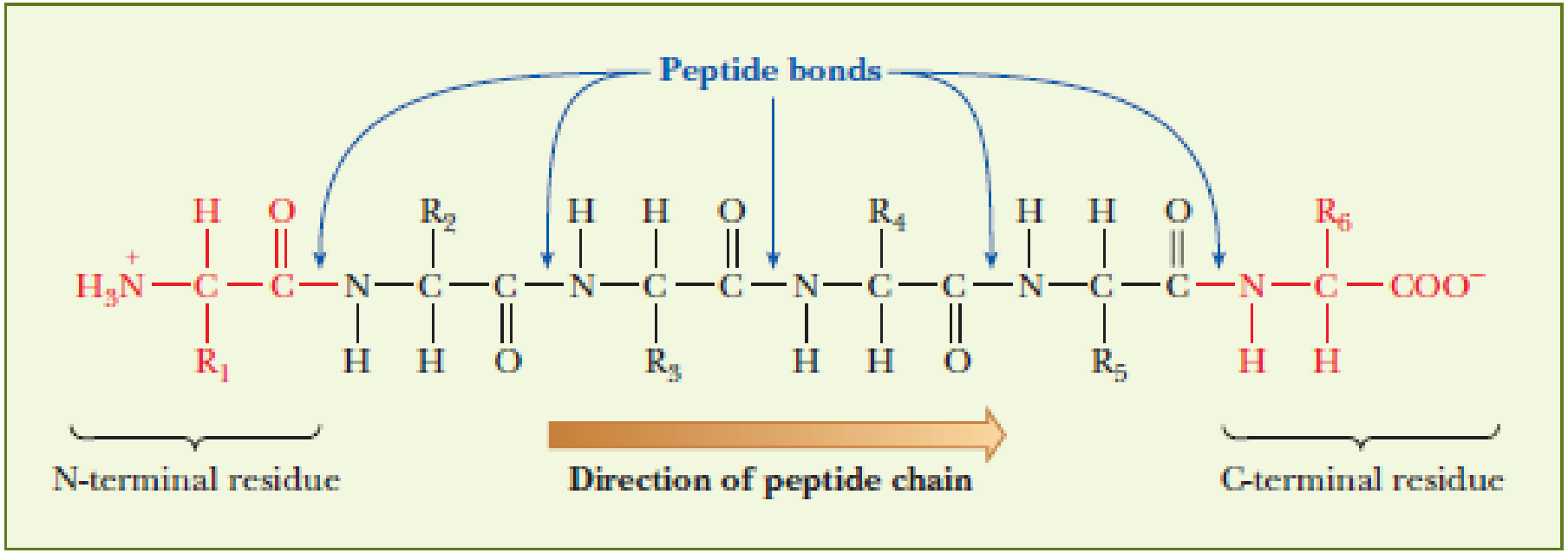
# Amino acid digestion and metabolism overview

# Amino Acid Structure

Only 20 are usually found in proteins



# Peptide and polypeptide chains




**Peptides:** two to several dozens AA.

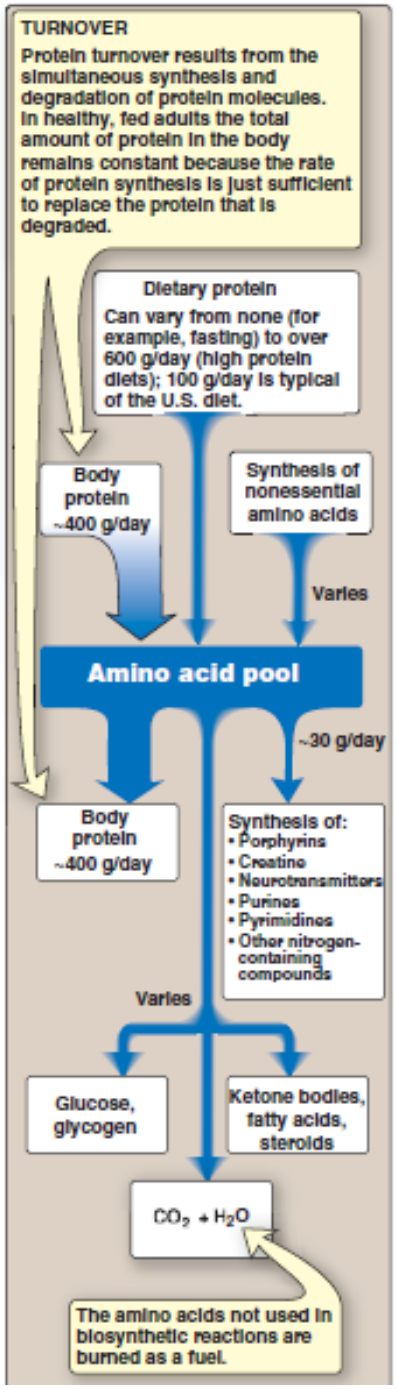
**Polypeptide chain:** many amino acids (usually more than a hundred)

# Amino acids (AAs)

- AAs are NOT stored in the body
- AAs sources are: diet, de novo synthesis or protein degradation
- AA metabolism overview:

1. α-amino group removal by transamination then oxidative deamination (N leaves the body as urea, ammonia or other compounds)
2. The resulting α-keto acids are converted to energy producing intemediates
3. Intermediate metabolism to $CO_2$, water, glucose, fatty acids, or ketone bodies

The metabolic processes have to keep harmony between amino acid pool and protein turn over



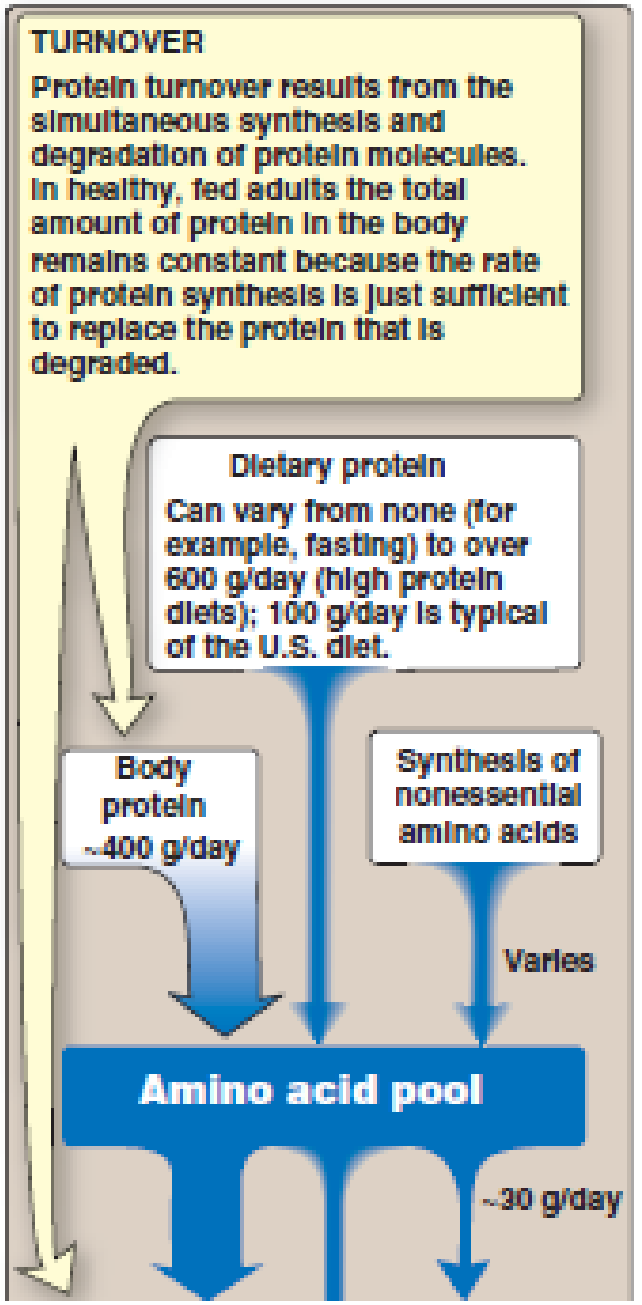

# Sources and fates of amino acids

- The AA pool is small ~about 90–100 g of AAs
- The amount of protein in the body is about 12 kg in a 70-kg man.
- Normally, the amount of AAs in the AA pool is balanced by the output (constant amount)
- The amino acid pool is in a steady state, and the individual is in nitrogen balance.

# Amino Acid Pool

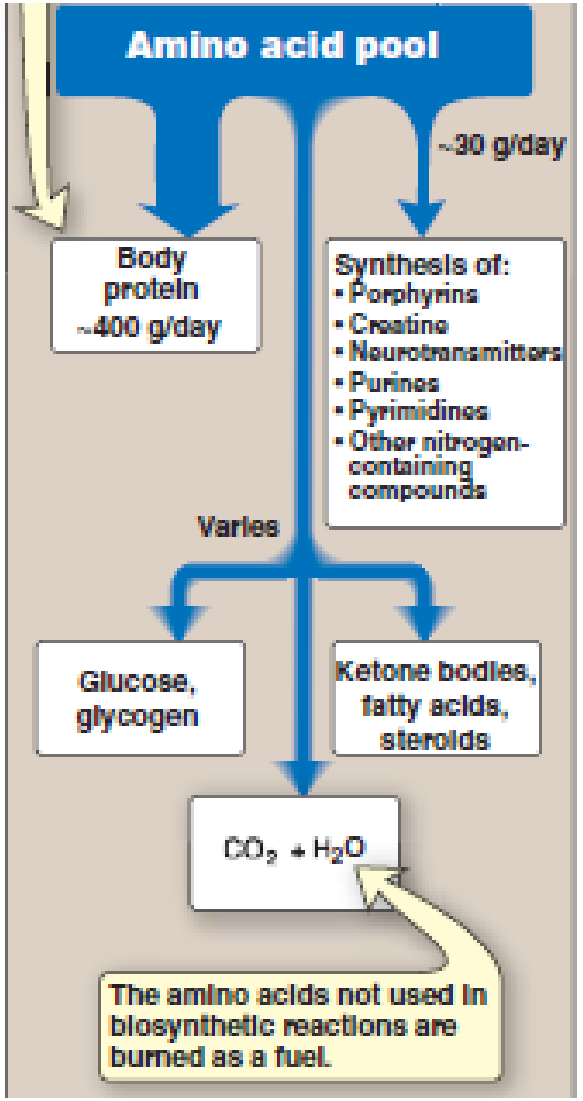
- AA sources:

1. Endogenous (body) protein degradation
2. Exogenous (dietary) protein digestion
3. Nonessential amino acids synthesized from metabolic intermediates



# Amino Acid Pool Depletion Routes

- AAs are depleted by 3 routes:
- 1) Synthesis of body protein
- 2) AAs consumed as precursors of nitrogen-containing small molecules
- 3) Conversion of AAs to glucose, glycogen, fatty acids, ketone bodies, or $CO_2 + H_2O$



# Protein Turnover

- Protein turnover is the process in which the rate of protein synthesis is sufficient to replace the degraded protein.
- Each day, 300–400 g of body protein is hydrolyzed and resynthesized
- In healthy adults, the total amount of protein in the body remains constant.
- Turnover varies widely for individual proteins.
- Most proteins are long-lived proteins (t1/2 days to weeks)
- Structural proteins, such as collagen, are metabolically stable (t1/2 months or years).

RATE OF PROTEIN TURNOVER

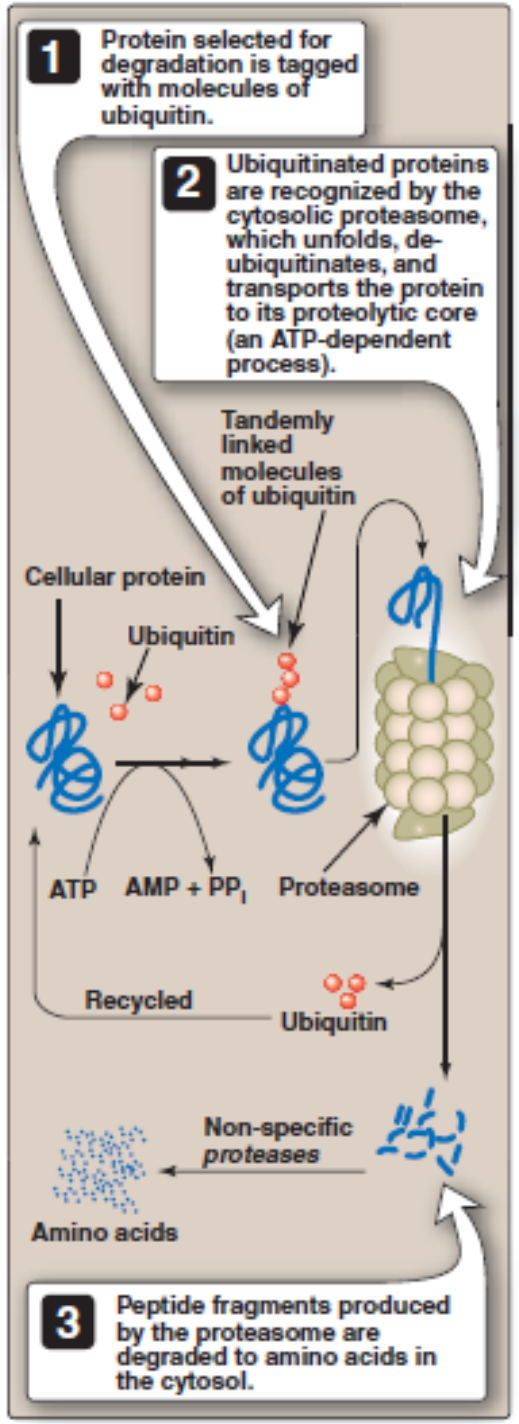
- For many proteins, regulation of synthesis determines the [protein in the cell] and protein degradation is minor
- For other proteins, the rate of synthesis is constitutive, or relatively constant, and [protein in the cells] is controlled by selective degradation.

# Protein degradation

Two major enzyme systems are responsible for degrading damaged or unneeded proteins:

1. The ATP-dependent ubiquitin-proteasome system of the cytosol mainly endogenous proteins (proteins that were synthesized within the cell)

2. The ATP-independent degradative enzyme system of the lysosome




# Ubiquitin-proteasome proteolytic pathway

**Ubiquitin** (Ub) is a small, globular, non-enzymic protein.

Several Ub units are added by an enzyme-catalyzed, ATP-dependent process to generate a **polyubiquitin chain**.

A proteasome is a large, barrel-shaped, macromolecular, proteolytic complex that recognizes Ub-protein

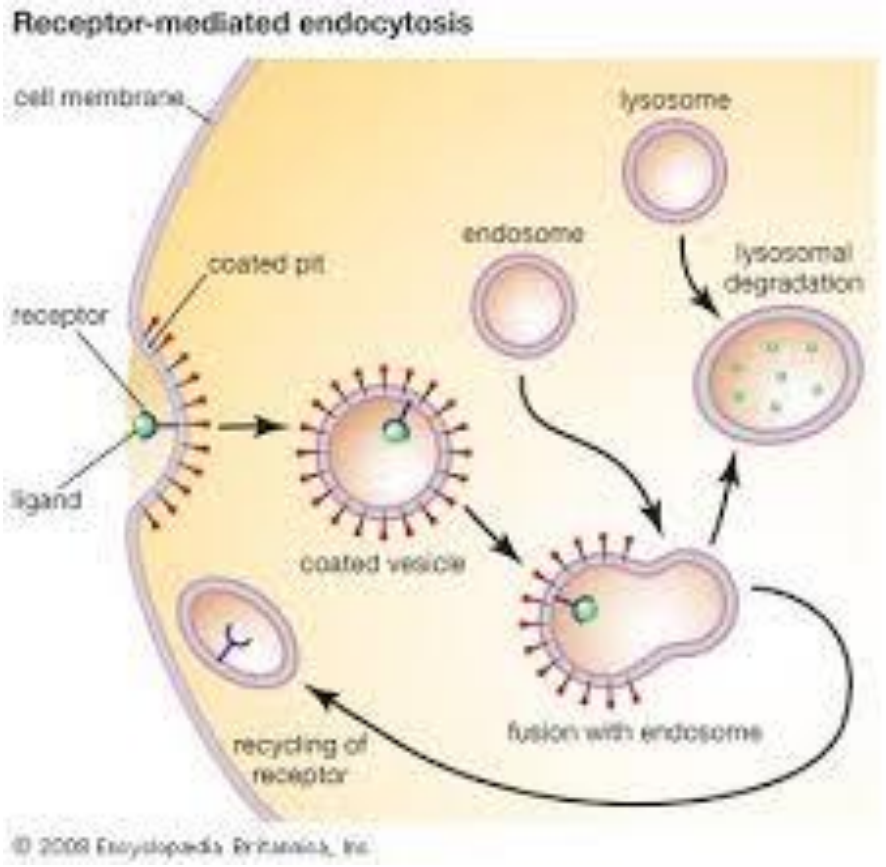
Simple hydrolysis by proteolytic enzymes does not require energy

# The ATP-independent degradative enzyme system of the lysosome

Lysosomal enzymes (acid hydrolases) degrade primarily:

A. Extracellular proteins, such as plasma proteins, by endocytosis

A. Cell-surface membrane proteins by receptor-mediated endocytosis.




www.Britannica.com

# DIGESTION OF DIETARY PROTEINS

70–100 g/day in the American diet

Proteins are too large to be absorbed by the intestine.

Protein digestion begins in the stomach

Stomach secretes the gastric juice that contains hydrochloric acid and the proenzyme, pepsinogen.

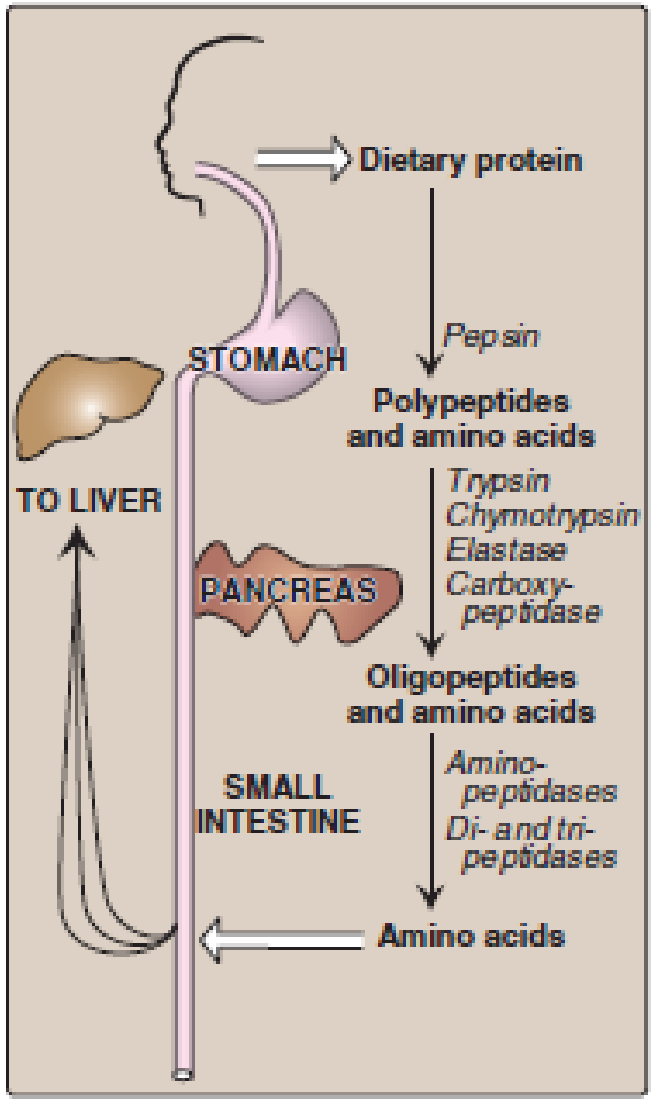
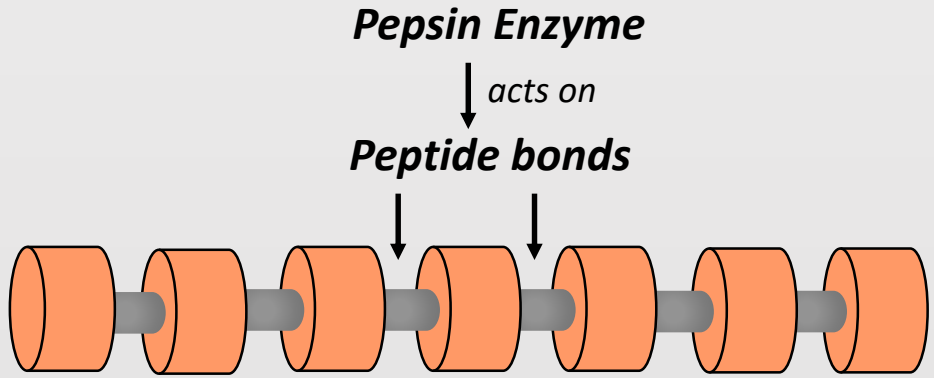



**Figure 19.4**
Digestion of dietary proteins by the proteolytic enzymes of the gastro-intestinal tract.

# Digestion of proteins by gastric secretion

1. **Hydrochloric acid:** pH 2–3 to hydrolyze proteins.




HCl is secreted by the parietal cells

HCl functions:

A. kills some bacteria
B. denatures proteins to make them more susceptible to subsequent hydrolysis by proteases.

**2. Pepsin:** acid-stable endopeptidase

- Is secreted by the chief cells of the stomach as an inactive zymogen (or proenzyme), pepsinogen.

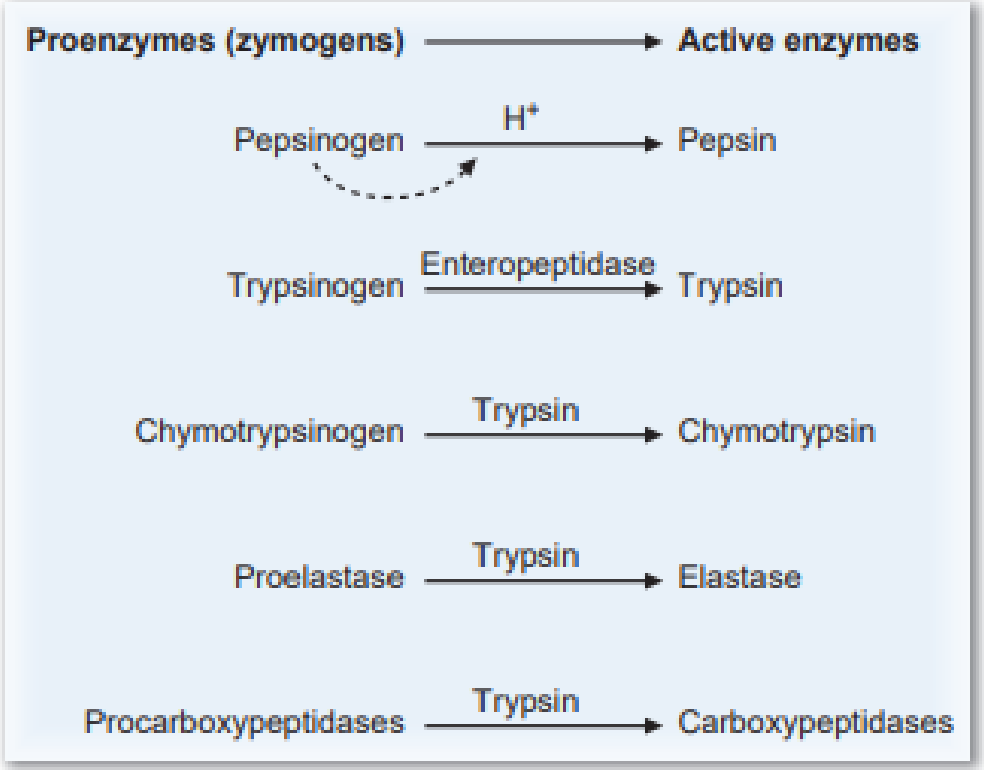
-Pepsinogen is activated to pepsin, either by HCl, or autocatalytically by other activated pepsin molecules.

-Pepsin releases peptides and a few free amino acids from dietary proteins.

# Digestion of proteins by pancreatic enzymes in small intestine

**Release of zymogens:** The release and activation of the pancreatic zymogens is mediated by the secretion of cholecystokinin and secretin (two polypeptide hormones of the GIT)

**Zymogen activation :** Enteropeptidase (enterokinase)— the luminal surface of intestinal mucosal cells converts the pancreatic zymogen trypsinogen to trypsin (removal of a hexapeptide from the N-terminus of trypsinogen)



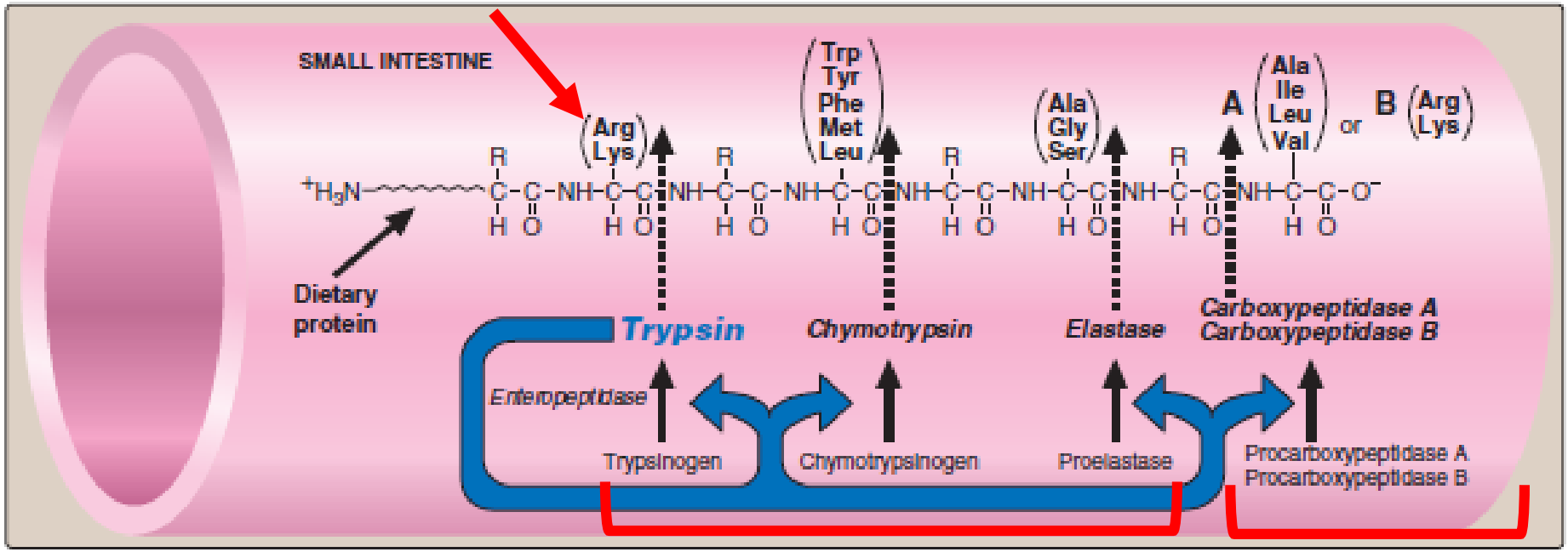

-Trypsin subsequently converts other trypsinogen molecules to trypsin

-Trypsin is the common activator of all pancreatic zymogens

# Digestion of proteins by pancreatic enzymes in small intestine

Large polypeptides produced in the stomach are further cleaved to oligopeptides and amino acids by a group of pancreatic proteases.

**Enzyme specificity:** Each of these enzymes has a different specificity for the amino acid R-groups adjacent to the susceptible peptide bond




Serine endopeptidases

Exopeptidases

# Digestion of oligopeptides by enzymes of the small intestine

Aminopeptidase at the luminal surface of the intestine

Aminopeptidase is an exopeptidase that repeatedly cleaves the N-terminal residue from oligopeptides to produce smaller peptides and free AAs.

The digestive enzymes digest themselves as well as dietary protein. They also digest the intestinal cells that are regularly sloughed off into the lumen.

# Absorption of amino acids and small peptides

Free AAs are absorbed into the enterocytes by a Na+-linked secondary transport system at the apical membrane.

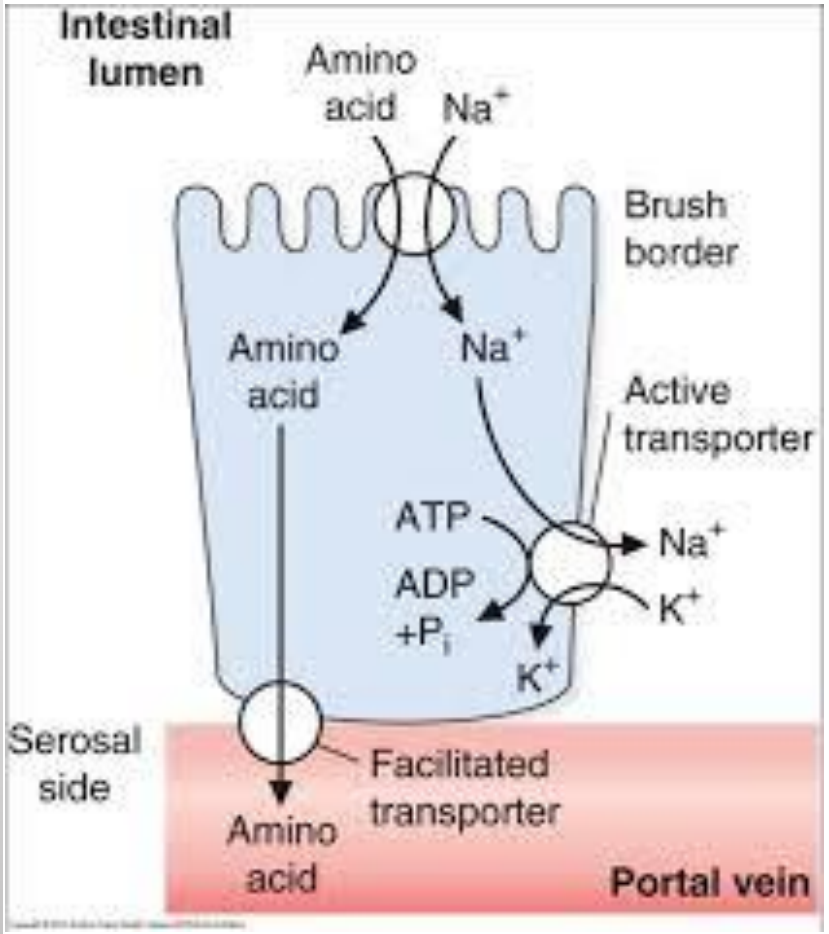
Di- and tri –peptides are absorbed by a H+-linked transport system.

The peptides are hydrolyzed in the cytosol to AAs

AAs are released into the portal system by facilitated diffusion.

AAs are either metabolized by the liver or released into the general circulation.

Branched-chain amino acids are not metabolized by the liver, but are sent from the liver to muscle via the blood

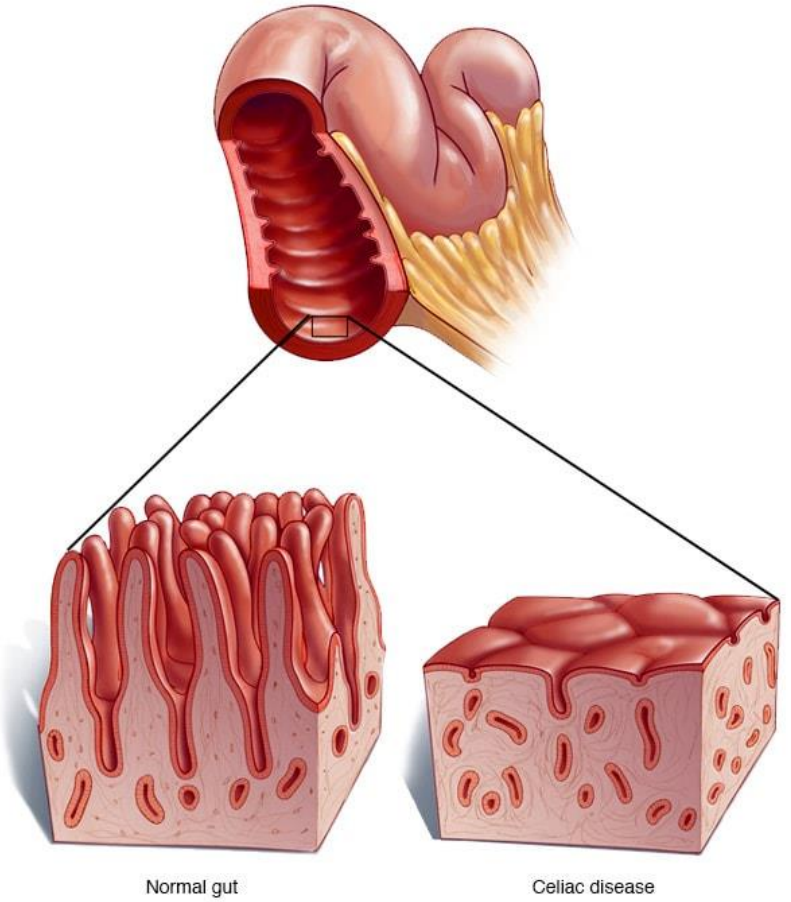


# Clinical Hint: Abnormalities in protein digestion and Celiac disease

Pancreatic secretion deficiency due to chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas, results in incomplete  fat and protein digestion.

Symptoms: abnormal appearance of lipids (**steatorrhea**), and **undigested protein** in the feces.

**Celiac disease** (celiac sprue) is a disease of **malabsorption** resulting from immune-mediated damage to the small intestine in response to ingestion of **gluten** (or gliadin produced from gluten), a protein found in wheat, barley and rye.



# Disposal of Nitrogen

# Transamination

**Substrate specificity of aminotransferases:**

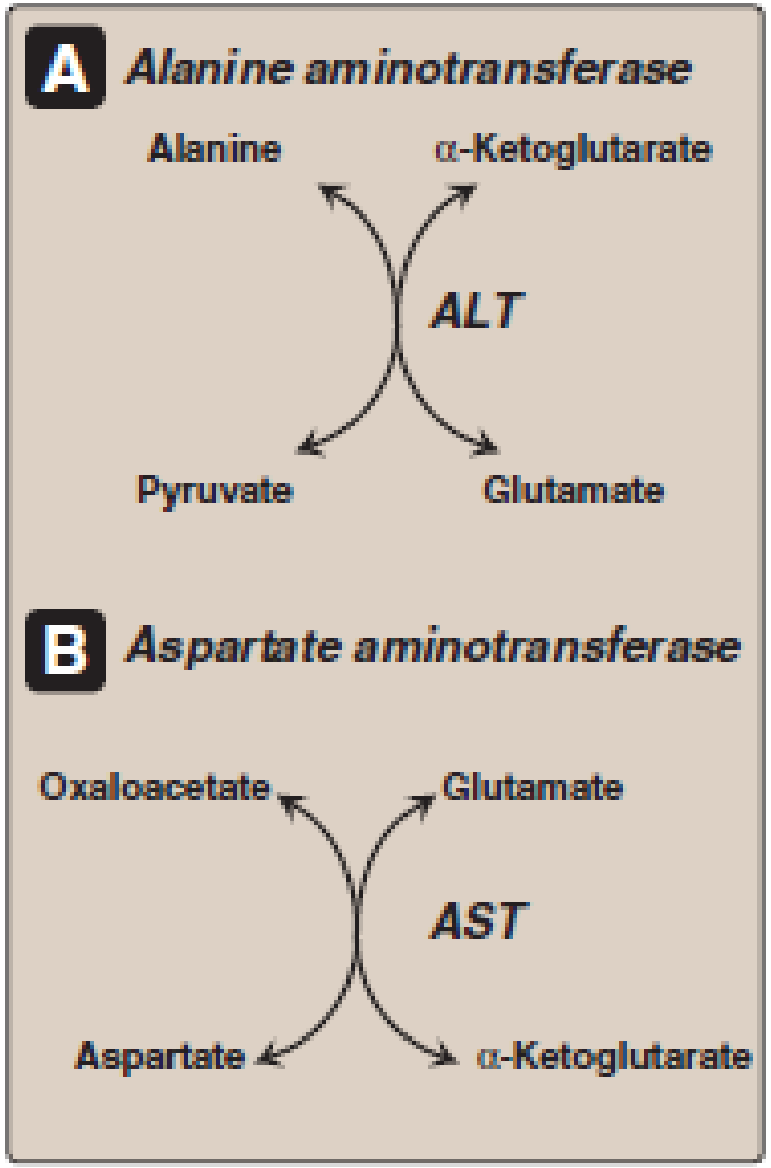
Each aminotransferase (AT) is specific for one or a few amino group donors.

The most important ATs are:

Alanine Aminotransferase (ALT)
Aspartate Aminotransferase (AST)

The equilibrium constant of transamination reactions is near one.

Keq=1 means the reaction functions in both amino acid degradation and biosynthesis according to the cellular needs



# Alanine aminotransferase (ALT)

ALT is present in many tissues.

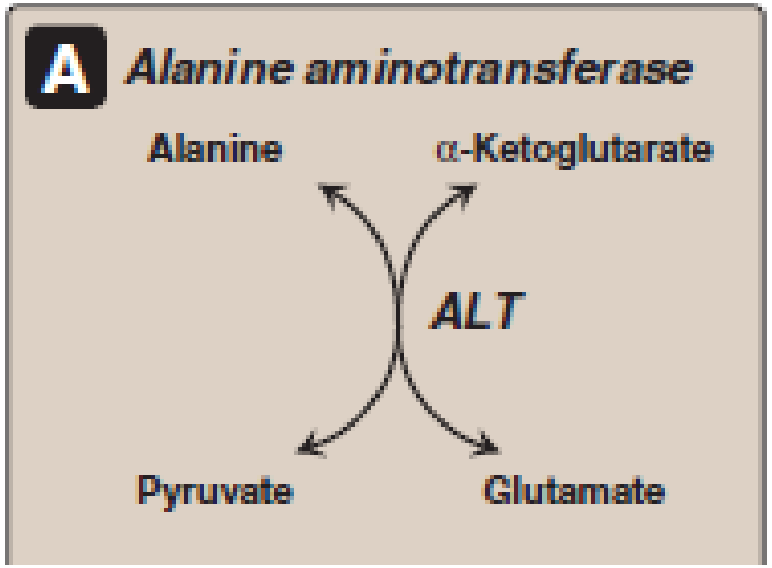
The enzyme catalyzes the transfer of the amino group of alanine to α-ketoglutarate

Reaction products: pyruvate and glutamate

The reaction is reversible.

During amino acid catabolism, ALT functions in the direction of glutamate synthesis.

Glu acts as a “collector” of nitrogen from Ala.



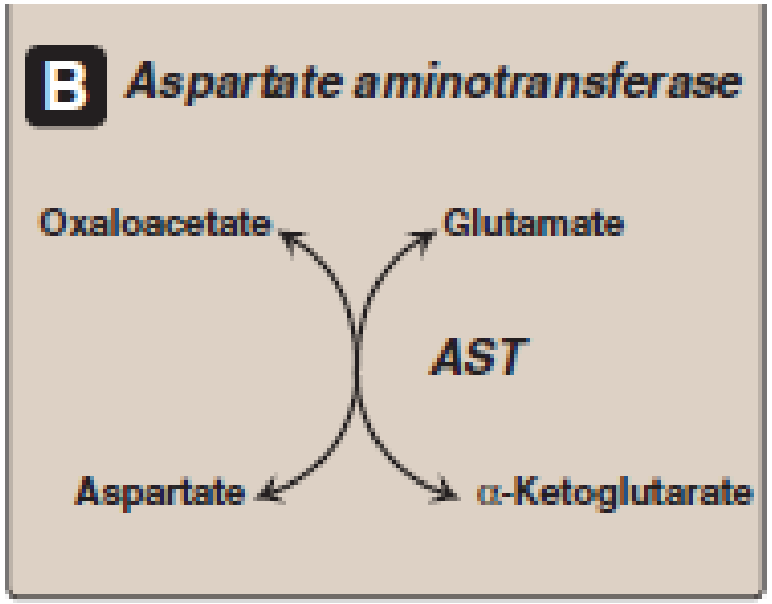
# Aspartate aminotransferase (AST)

AST does not funnel amino groups to form Glu

During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate.

Aspartate is used as a source of nitrogen in the urea cycle

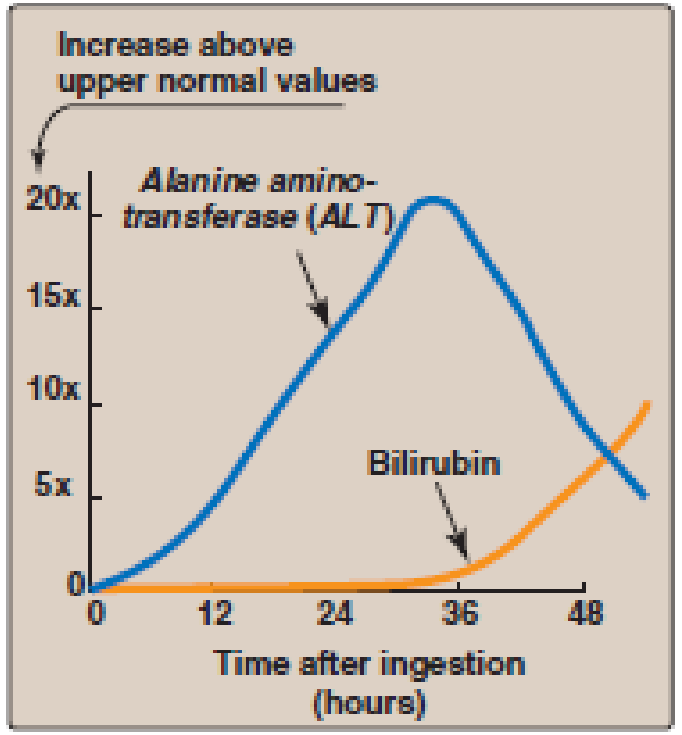
The AST reaction is reversible



# Clinical hint: Diagnostic value of plasma aminotransferases

ATs are normally intracellular enzymes but low levels in the plasma represent the release of cellular contents during normal cell turnover.

AST and ALT have a diagnostic value when found in the plasma.




**a. Liver disease:** Plasma AST and ALT are elevated
Examples: severe viral hepatitis, toxic injury, and prolonged circulatory collapse.
ALT is more specific than AST for liver disease
AST is more sensitive because the liver contains larger amounts of AST.

**b. Nonhepatic disease:** MI and muscle disorders.

# Oxidative deamination of amino acids

Oxidative deamination by glutamate dehydrogenase results in the liberation of the amino group as free ammonia (NH3)

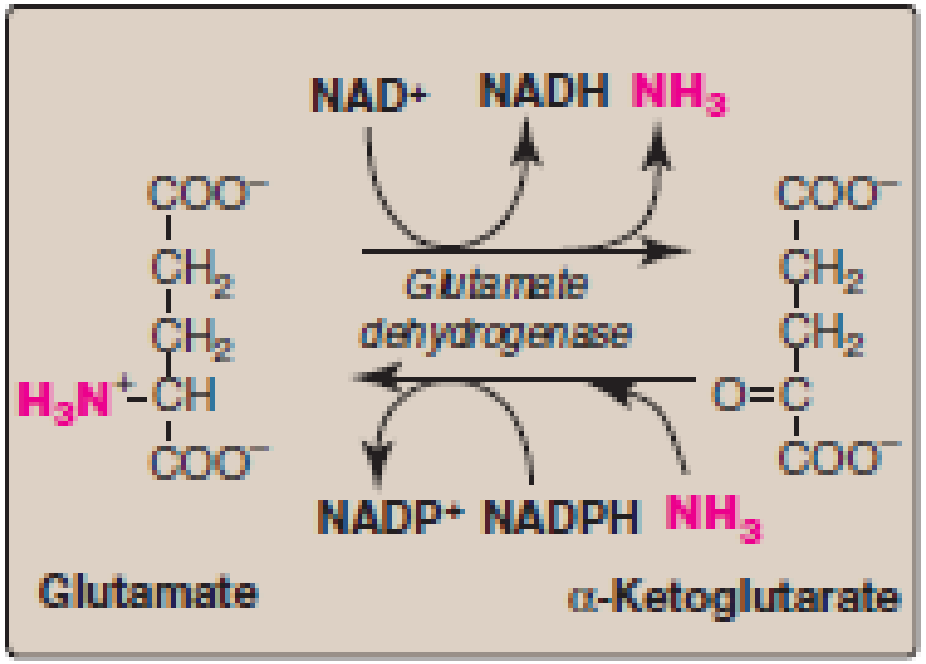
Glutamate is the only amino acid that undergoes rapid oxidative deamination

Reactions occur primarily in the liver and kidney.

Reaction products:

1. α-keto acids that can enter the central pathway of energy metabolism

2. ammonia, the source of nitrogen in urea synthesis.




**Allosteric regulators of glutamate dehydrogenase:**

GTP is an allosteric inhibitor
ADP is an activator.

# D-Amino acid oxidase

D-Amino acids are found in plants and in the cell walls of microorganisms

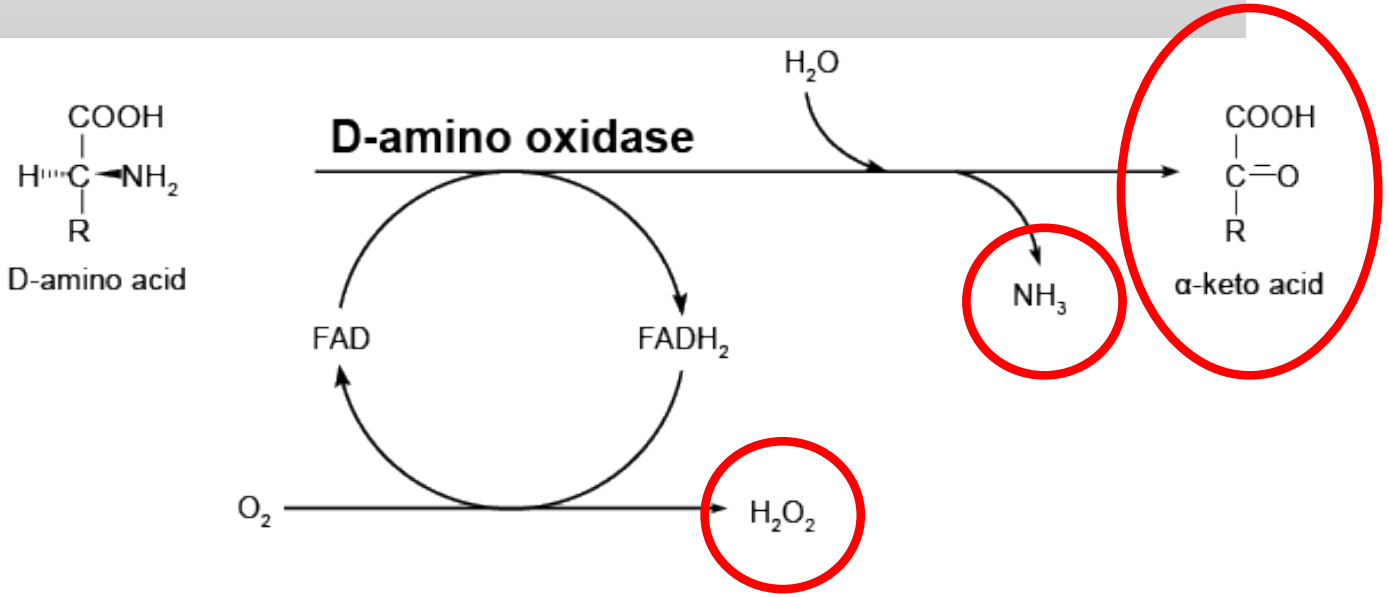
No D-amino acids in mammalian proteins

D-Amino acid metabolism by the kidney and liver.

D-Amino acid oxidase (DAO) is an FAD-dependent peroxisomal enzyme that catalyzes the oxidative deamination of D-amino acids

Increased DAO activity has been linked to increased susceptibility to schizophrenia.

L-amino acid oxidases are components of several snake venoms.



# Metabolism of ammonia

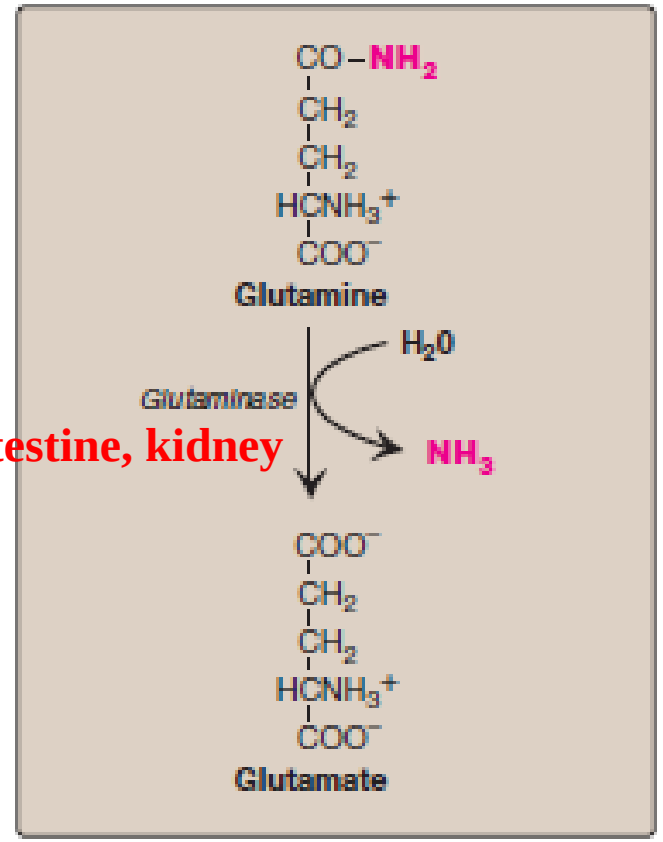
# Sources of ammonia

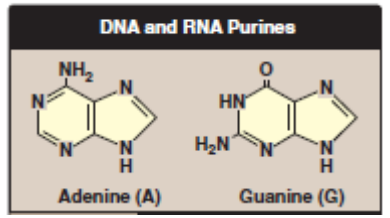
1. **From glutamine:** Most of this ammonia is excreted into the urine as $NH_4^+$ (acid –base balance)

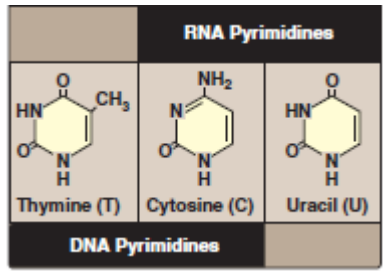
**2. From bacterial action in the intestine:** Ammonia is formed from urea in the intestinal lumen by the bacterial urease.
This NH3 is absorbed from the intestine by the portal vein and is converted to urea by the liver.

**3. From amines:** Amines in the diet, and monoamines that act as hormones or neurotransmitters, give rise to NH3 by amine oxidase

**4. From purines and pyrimidines:** In the catabolism of purines and pyrimidines, amino groups attached to the rings are released as NH3



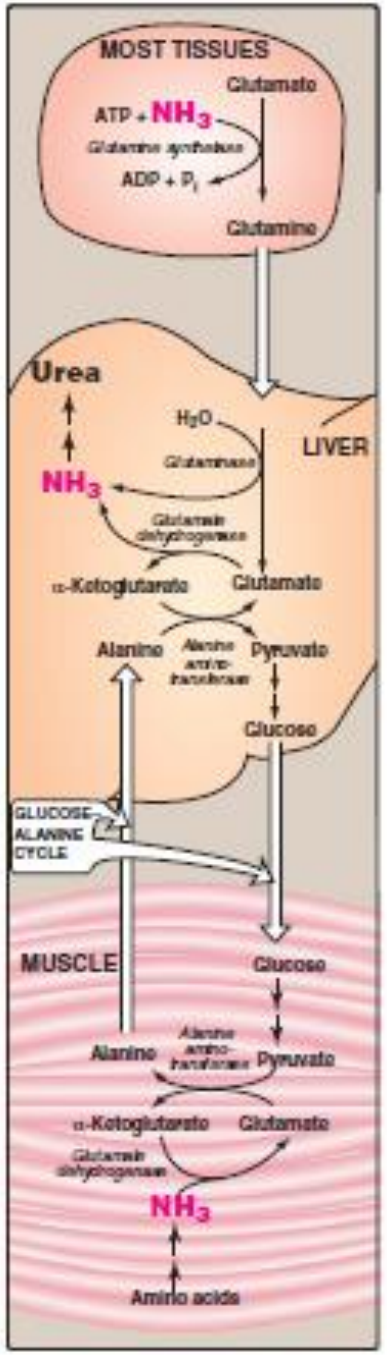
# Transport of ammonia to the liver

$NH_3$ is transported from peripheral tissues to liver for conversion to urea.

Two mechanisms for ammonia transport:

1. By glutamine synthetase that combines $NH_3$ with Glu to form Gln
- Found in most tissues
- Requires energy
- A nontoxic transport form of ammonia
- The resulting glutamine is transported in the blood to the liver to be cleaved by glutaminase to produce glutamate and free ammonia

2. By transamination of pyruvate to form alanine
- Primarily in muscles
- Alanine is transported by the blood to the liver to be converted to pyruvate by transamination.
- Pyruvate can be used in gluconeogenesis (glucose-alanine cycle)



# UREA CYCLE

Urea is a major disposal form of amino groups derived from AAs.

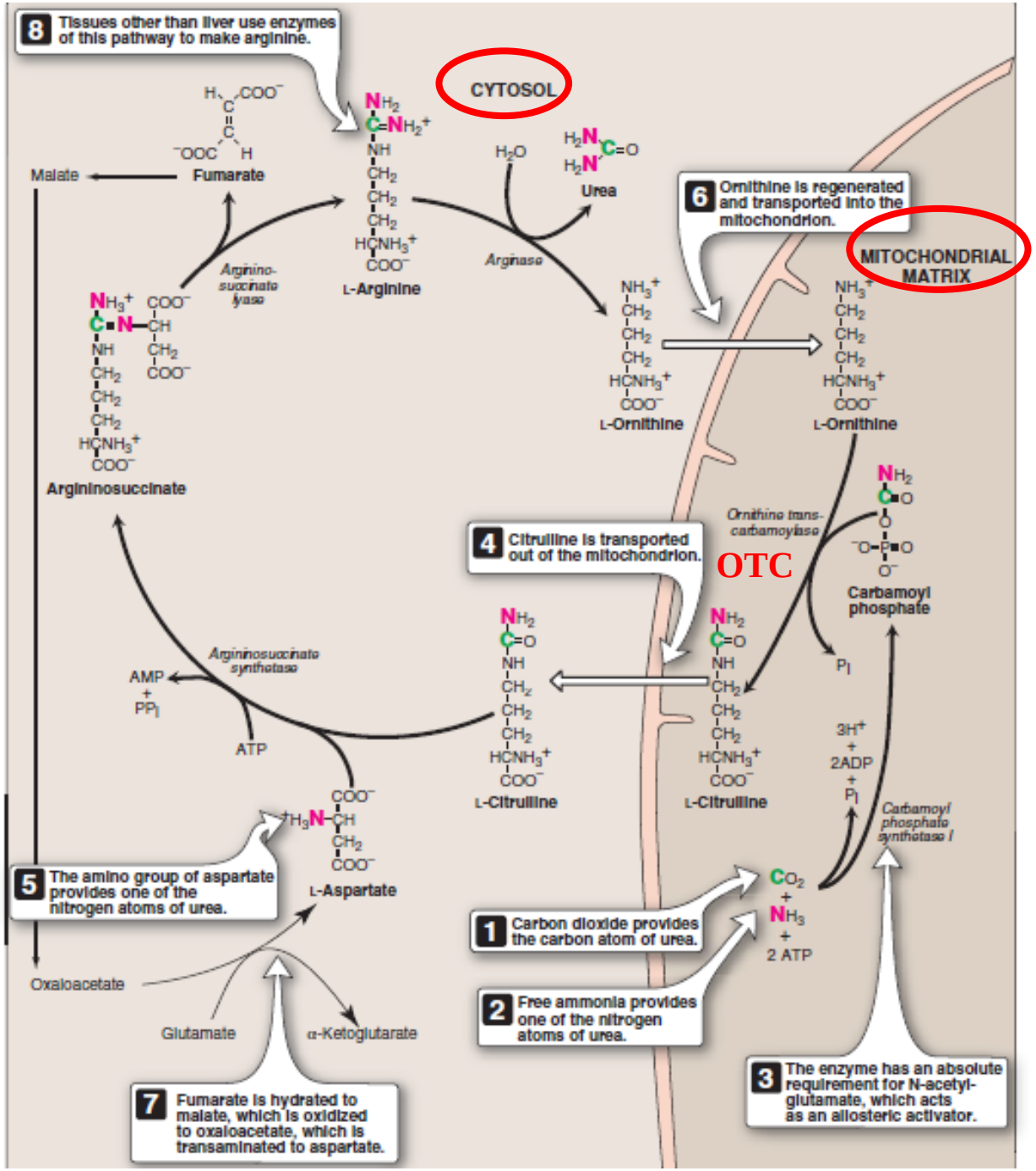
Urea accounts for about 90% of the N-containing components of urine.

One N of urea molecule is supplied by free ammonia (from oxidative deamination of Glu), and the other N by Asp.

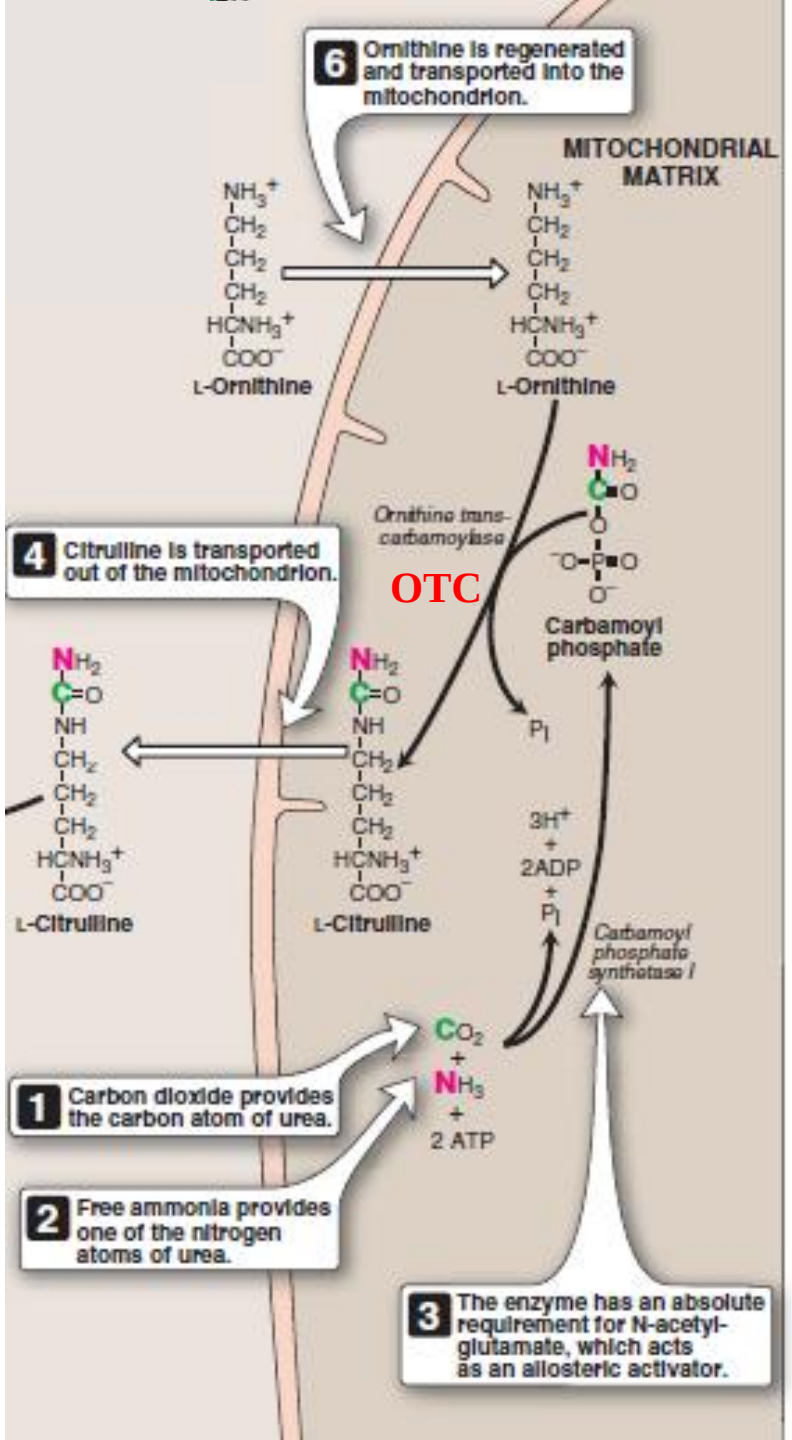
The C and O of urea are derived from $CO_2$.

Urea is produced by the liver

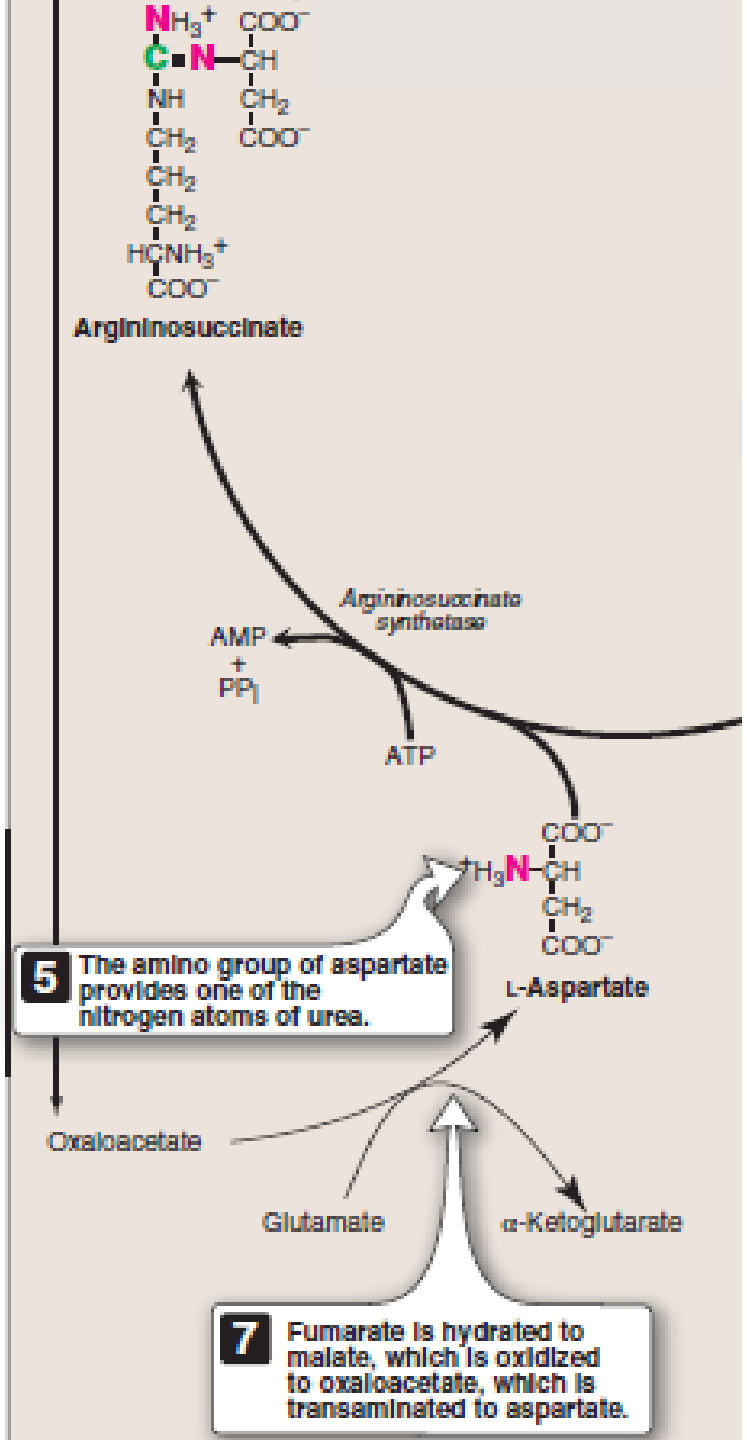
Urea is transported in the blood to the kidneys for excretion in the urine.

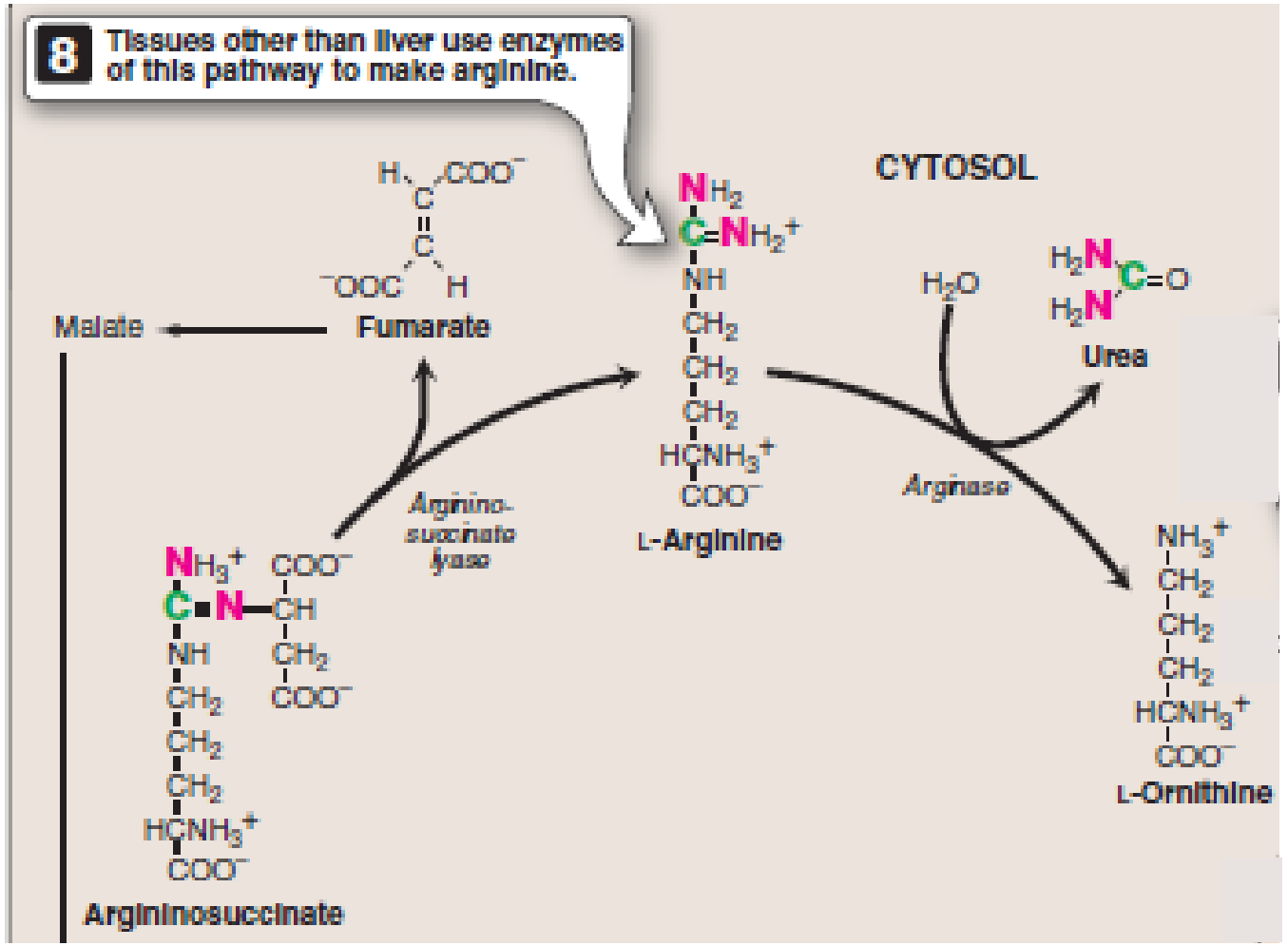


# In the mitochondria



# In the cytosol



# Overall stoichiometry of the urea cycle

$$\text{Aspartate} + NH_3 + CO_2 + 3\,ATP + H_2O \longrightarrow$$

$$\text{urea} + \text{fumarate} + 2\,ADP + AMP + 2\,P_i + PP_i$$

The synthesis of urea is irreversible, with a large, negative ΔG

For each urea molecule:

1. Four high-energy P-bonds
2. One nitrogen of the urea molecule is supplied by free NH3
3. The other nitrogen is supplied by aspartate.
4. Glutamate is the precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).

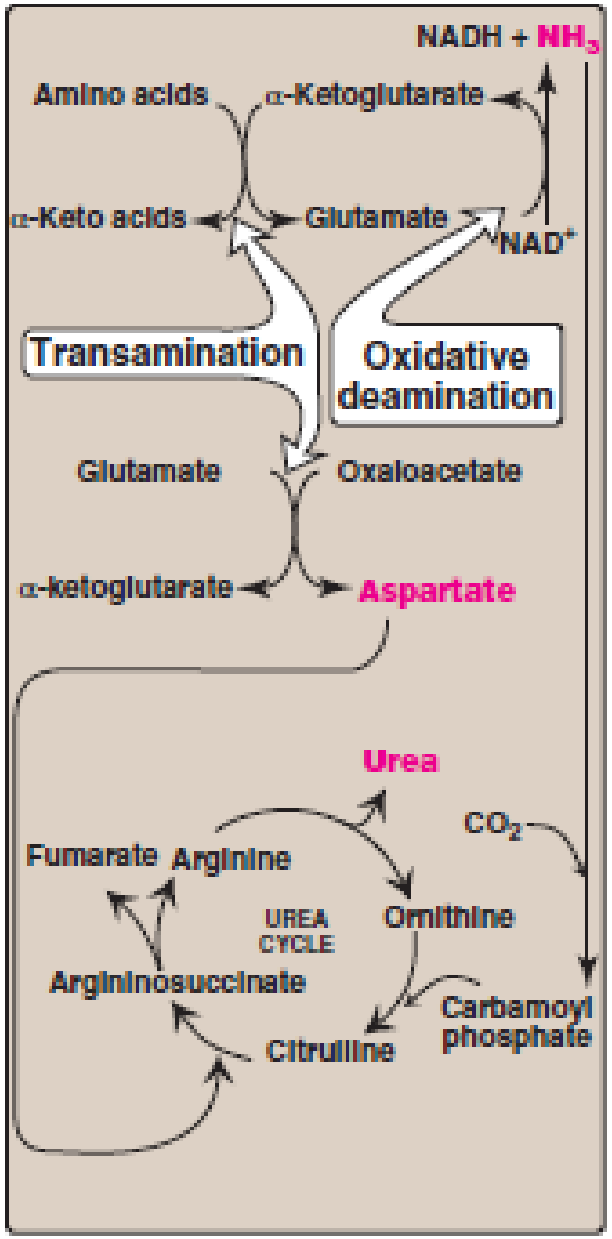
# Regulation of the urea cycle

N-Acetylglutamate is an essential **activator** for carbamoyl phosphate synthetase I—the rate-limiting step in the urea cycle

Arginine is an **activator** for N-Acetylglutamate synthesis

The intrahepatic concentration of N-acetylglutamate increases after a protein-rich meal (more glutamate and arginine are provided)

More protein in diet leads to increased urea synthesis rate



# Clinical hint: Hyperammonemia

NH3 has a neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision). At high concentrations, ammonia can cause coma and death.

Types:

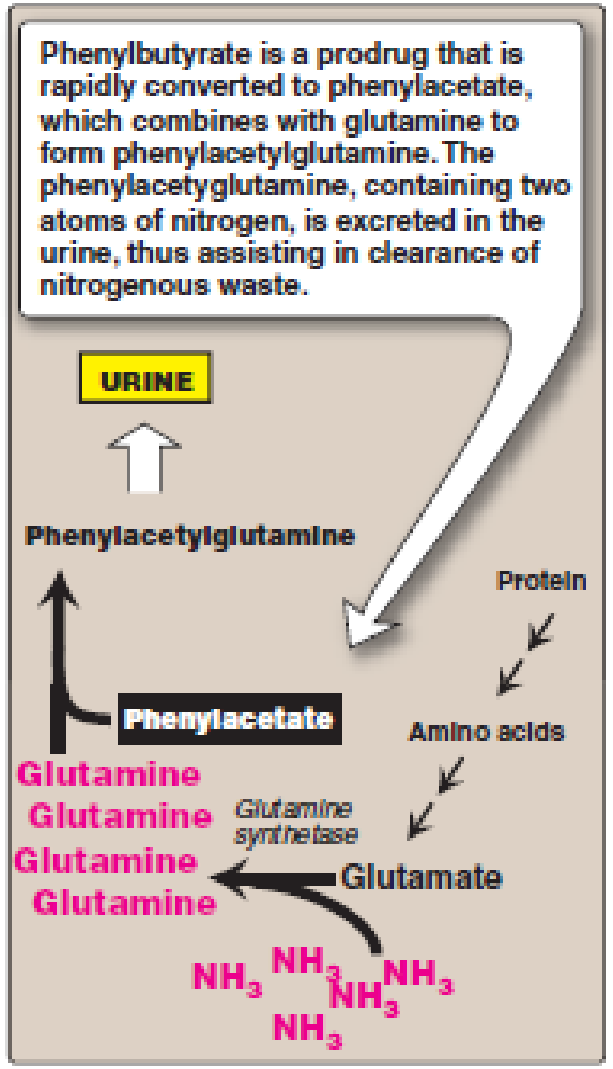
**Acquired hyperammonemia:** Liver disease due to viral hepatitis, or to hepatotoxins such as alcohol.

**Congenital hyperammonemia:** Genetic deficiencies of any of the five enzymes of the urea cycle leads to failure to synthesize urea

The overall prevalence estimated to be 1:25,000 live births.

Ornithine transcarbamoylase deficiency is the most common

Treatment: restriction of dietary protein, administration of compounds that bind covalently to AAs, producing nitrogen-containing molecules that are excreted in the urine



# Amino Acid Carbon Skeleton Degradation

# GLUCOGENIC AND KETOGENIC AMINO ACIDS

Seven intermediates are produced during AA catabolism (**oxaloacetate, pyruvate, α-ketoglutarate, fumarate, succinyl coenzyme A (CoA), acetyl CoA, and acetoacetate**).

**Glucogenic amino acids** catabolism yields pyruvate or one of the TCA cycle intermediates that can be used as substrates for gluconeogenesis in the liver and kidney.

**Ketogenic amino acids** catabolism yields either acetoacetate (a type of ketone bodies) or one of its precursors (acetyl CoA or acetoacetyl CoA).

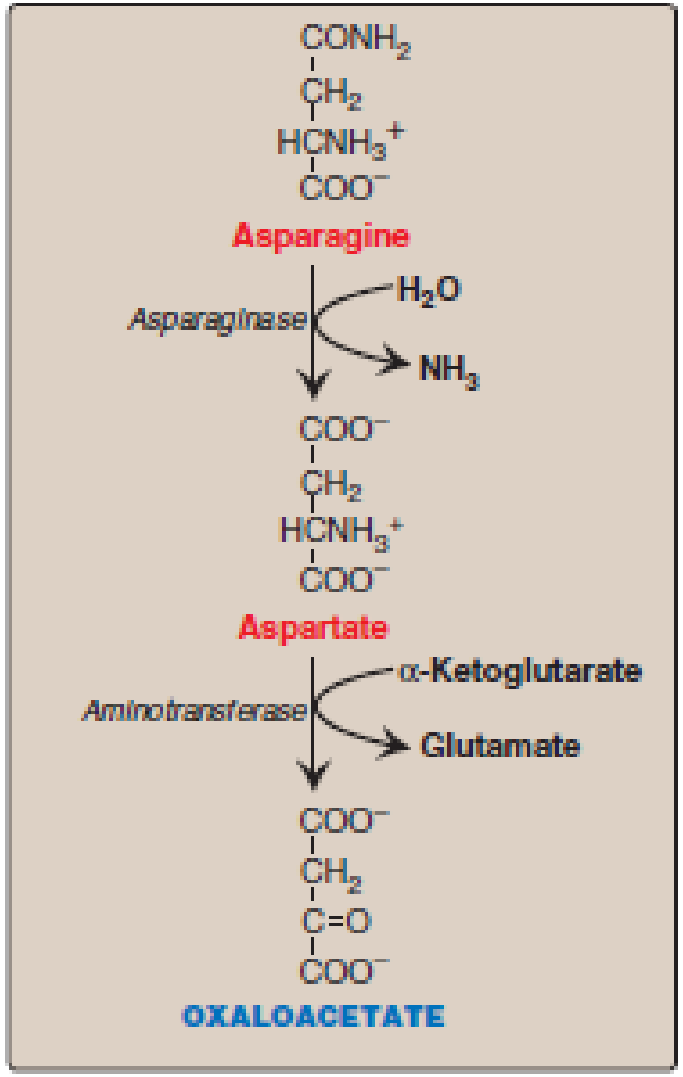
Other ketone bodies are 3-hydroxybutyrate and acetone

| | Glucogenic | Glucogenic and Ketogenic | Ketogenic |
|---|---|---|---|
| Nonessential | Alanine<br>Arginine<br>Asparagine<br>Aspartate<br>Cysteine<br>Glutamate<br>Glutamine<br>Glycine<br>Proline<br>Serine | Tyrosine | |
| Essential | Histidine<br>Methionine<br>Threonine<br>Valine | Isoleucine<br>Phenyl-alanine<br>Tryptophan | Leucine<br>Lysine |

# 1. Amino acids that form oxaloacetate

**Hydrolysis**

**Transamination**



# 2. Amino acids that form α-ketoglutarate via glutamate

| | | | |
|---|---|---|---|
| **Glutamine** | **Proline** | **Arginine** | **Histidine** |

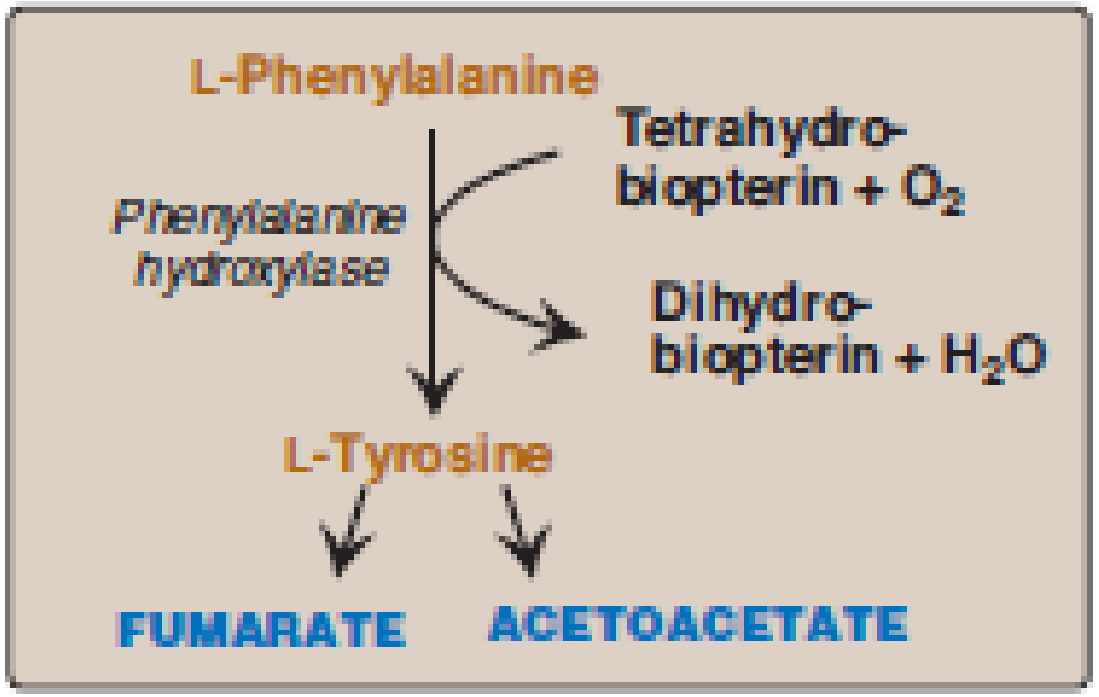
# 3. Amino acids that form <u>fumarate</u>

**Phenylalanine and tyrosine:**

Hydroxylation of phenylalanine produces tyrosine

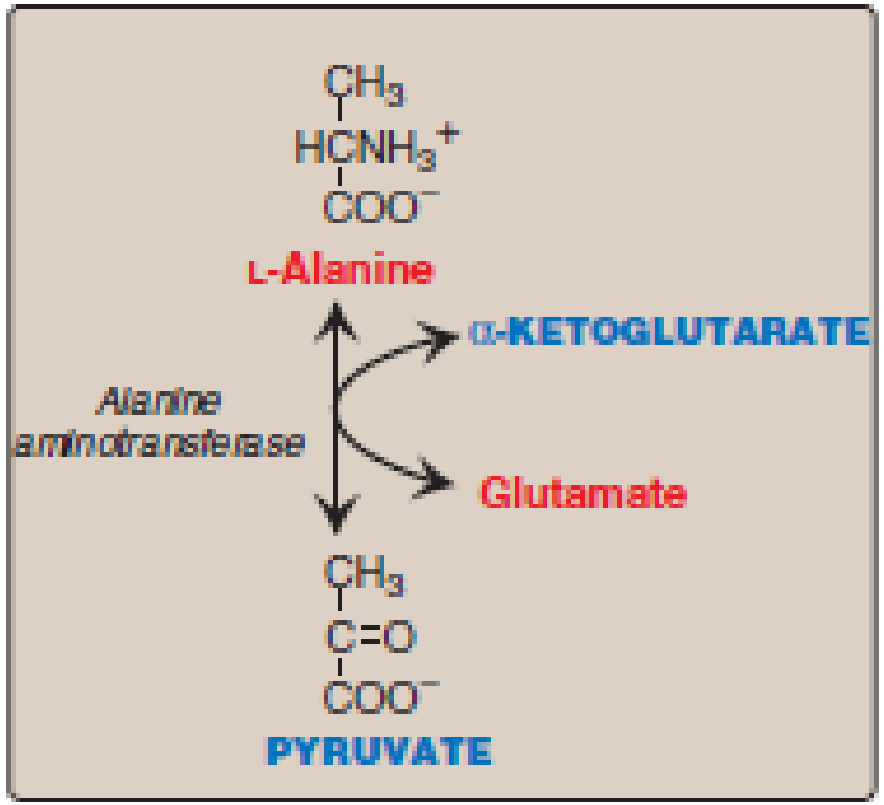
Phenylalanine and tyrosine are both glucogenic and ketogenic.

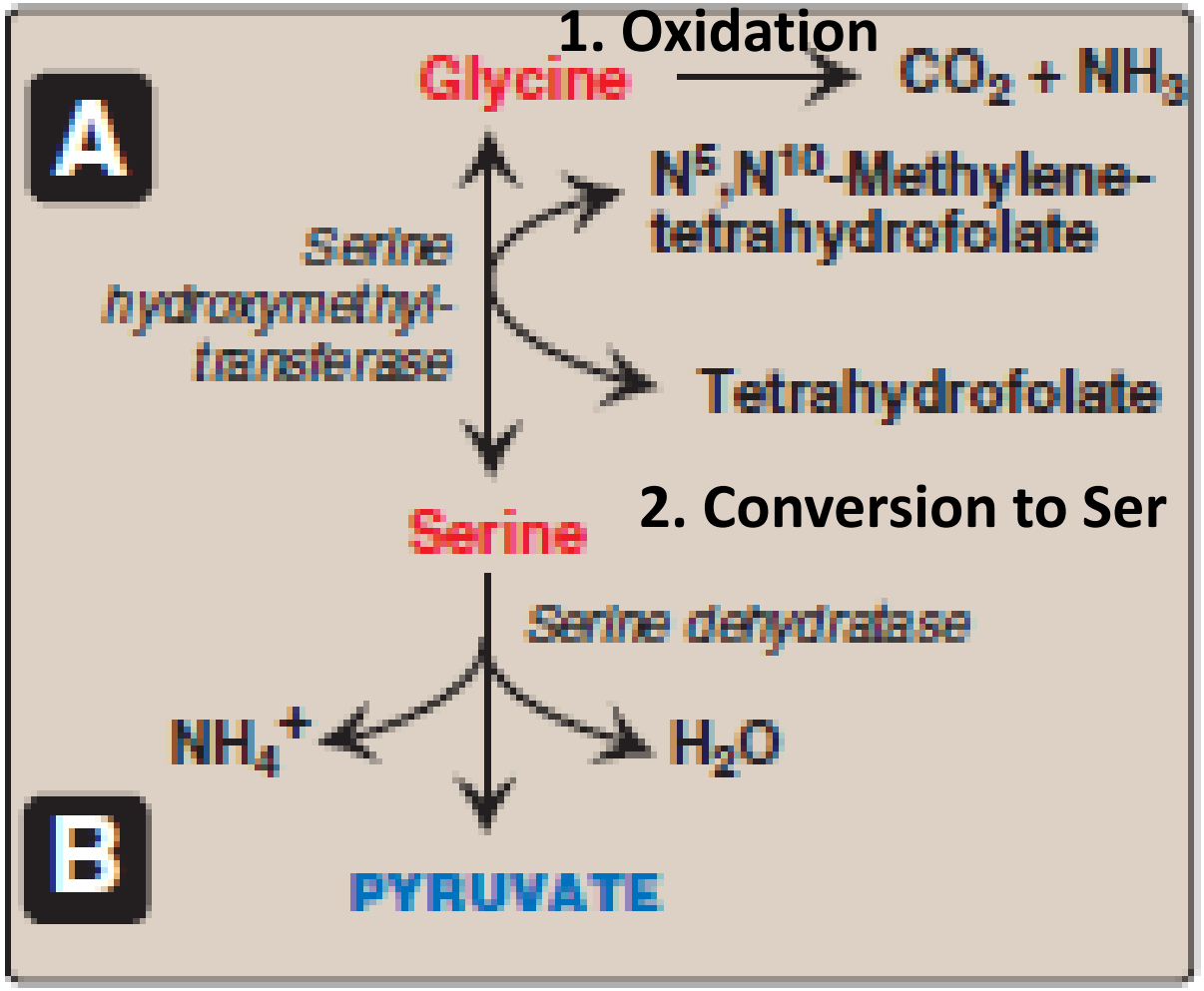
Inherited deficiencies in the enzymes that metabolize Phe and Tyr lead to **phenylketonuria, alkaptonuria and albinism**



# 4. Amino acids that form pyruvate

## Alanine



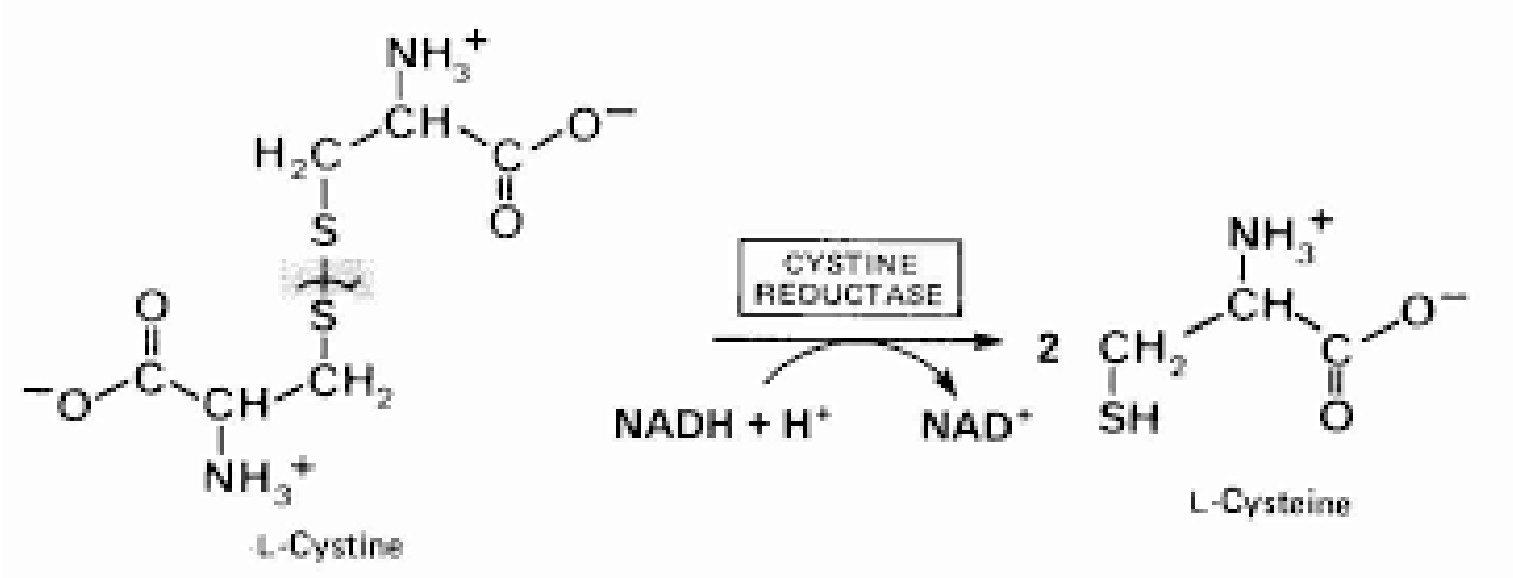



# 4. Amino acids that form <u>pyruvate</u>

**Cystine** is reduced to cysteine

NADH + H+ act as a reductant.

**<u>Cysteine</u>** desulfuration yields pyruvate.




**Threonine** is converted to pyruvate or to α-ketobutyrate, which forms succinyl CoA.

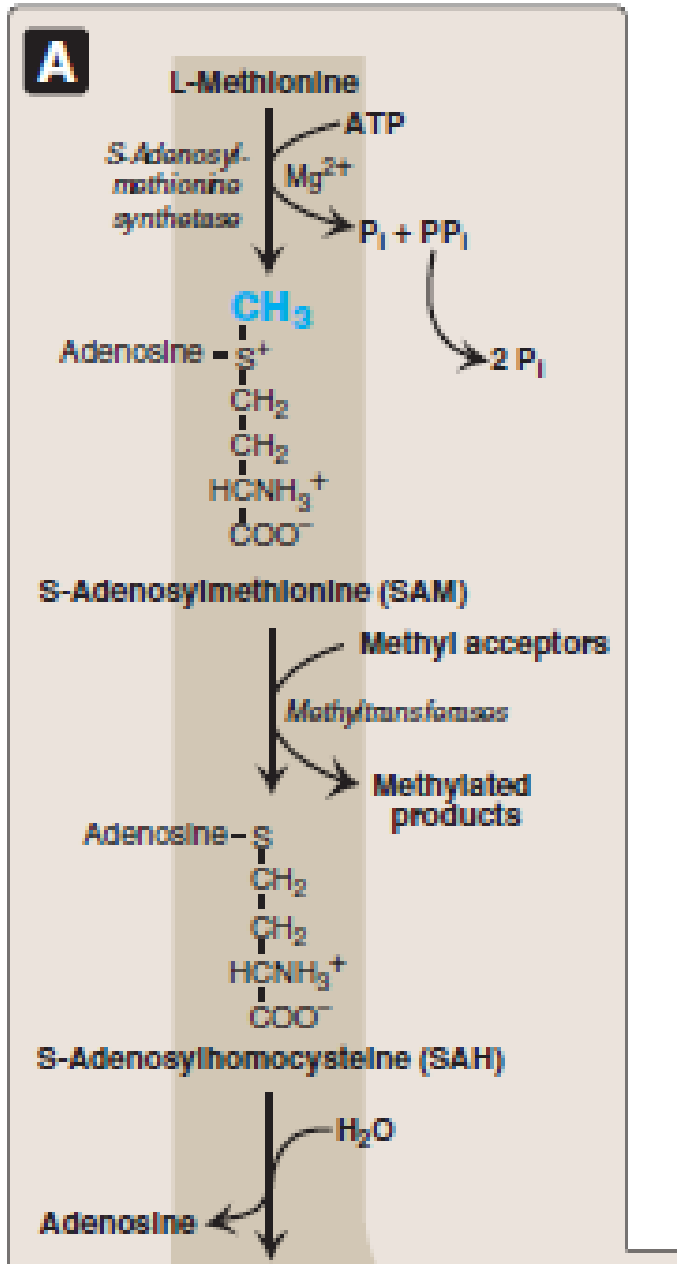
# 5. Amino acids that form succinyl CoA
## (a TCA cycle intermediate and glucogenic compound)

**Valine and isoleucine are** branched-chain amino acids
They generate propionyl CoA that is converted to succinyl CoA by biotin- and vitamin B12–requiring reactions

**Threonine** is dehydrated to α-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA.
Thr can also be converted to pyruvate.

**Methionine** is converted to S-adenosyl methionine (SAM), the major methyl-group donor in one-carbon metabolism.

# Methionine Metabolism




**1. Synthesis of SAM (**a high-energy compound that has no phosphate) requires energy (ATP)

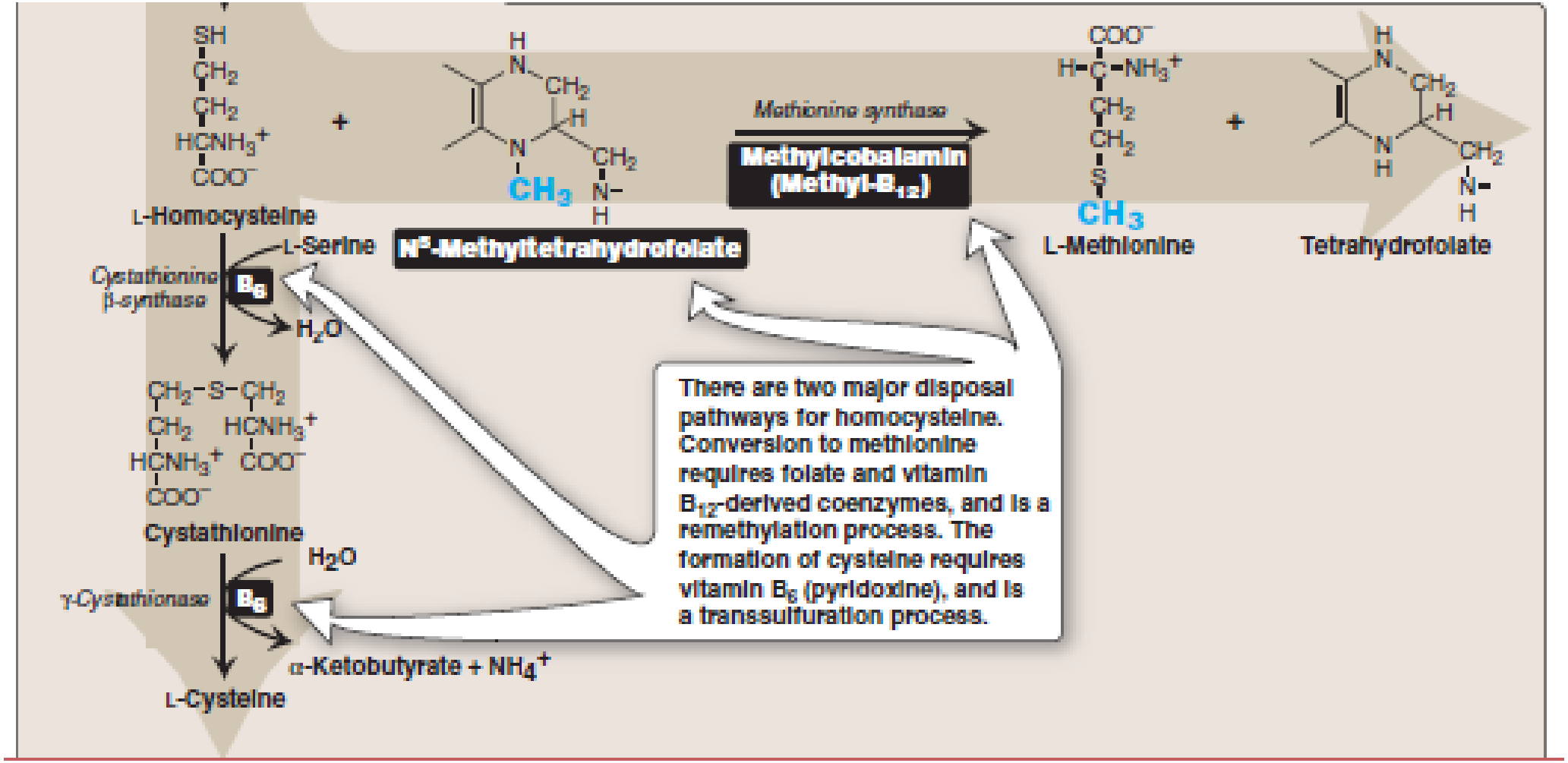
**2. Methyl group activation** to be ready for transfer to acceptor molecules, such as norepinephrine in the synthesis of epinephrine.
Methyl group is transferred to O, N, or C atoms.
Methyl transfer is irreversible because of free energy loss.

**3. Hydrolysis of SAH** to homocysteine and adenosine.

Homocysteine fates:

A. Remethylation if Met is deficient
B. Transulfuration pathway if Met is available to be converted to Cys

# Synthesis of cysteine and methionine



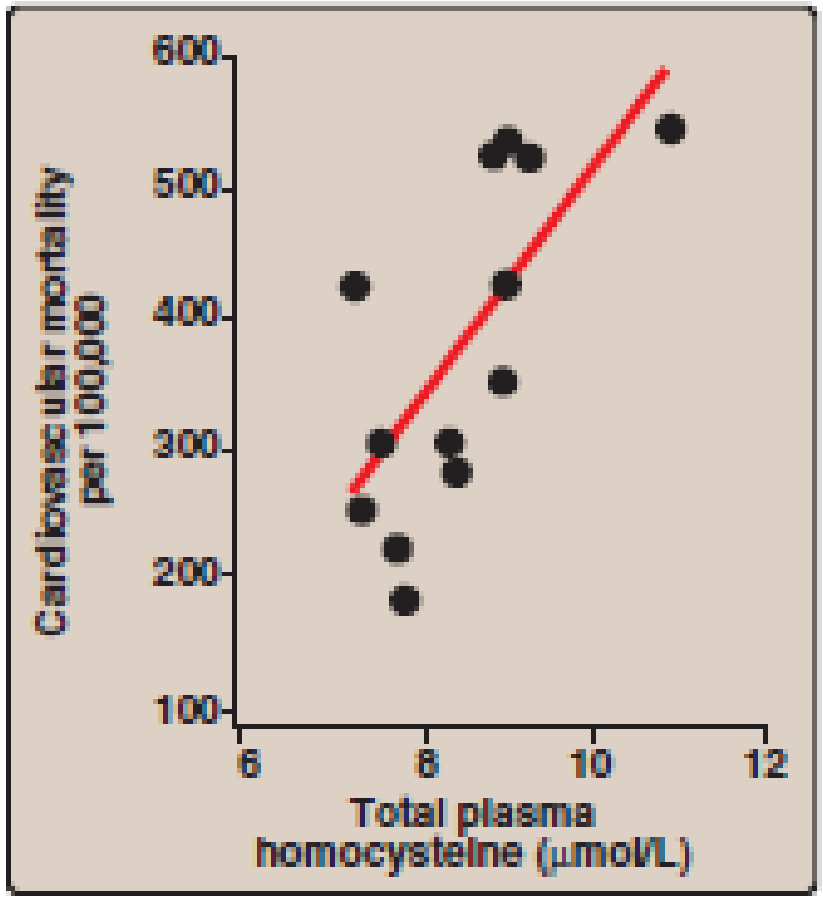

The resulting α-ketobutyrate is oxidatively decarboxylated to form propionyl CoA that is then converted to succinyl CoA.

# Clinical hint: Homocysteine and vascular disease

High homocysteine promote oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease

Homocysteine levels are inversely related to levels of folate, B12, and B6.

Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.



# 6+7. Amino acids that form acetyl CoA or acetoacetyl CoA

Phe and Tyr produce acetoacetate during their catabolism

**Leucine** is exclusively ketogenic (acetoacetate and acetyl CoA)

**Isoleucine** is both ketogenic and glucogenic (acetyl CoA, acetoacetyl CoA and succinyl CoA)

**Lysine** is an exclusively ketogenic (acetyl CoA and acetoacetyl CoA).

**Tryptophan** is both glucogenic and ketogenic (acetyl CoA and acetoacetyl CoA)

# Branched chain amino-acids (Leu, Val, Ile)

- Essential amino acids
- Important for the synthesis of excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA)
- In contrast to other amino acids, they are metabolized primarily by the peripheral tissues (particularly muscle), rather than by the liver
- Are metabolized by a similar route of metabolism
- Transamination, oxidative decarboxylation, dehydrogenation and then end product formation

# Amino Acid Synthesis

# Biosynthesis of Nonessential Amino Acids

Essential: Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His

Nonessential: Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, Pro, Ser & Tyr

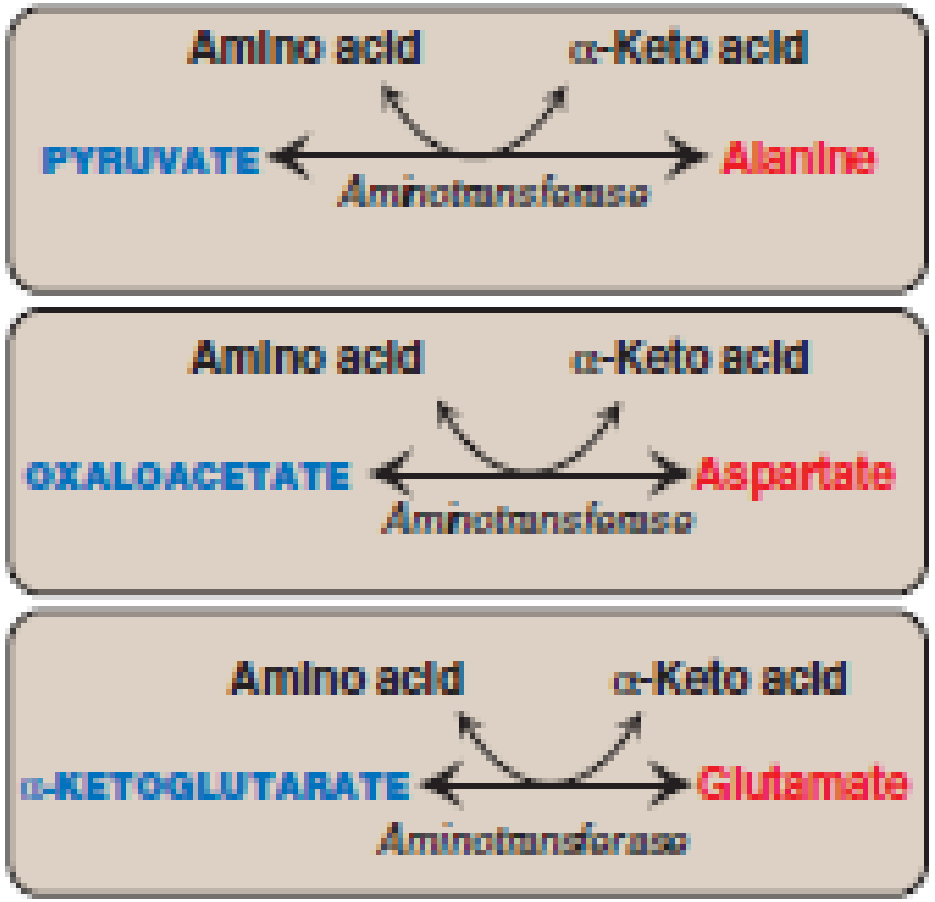
Nonessential amino acids are synthesized from:

1. Metabolic intermediates

2. Or from the essential amino acids.

    Example: Tyr and Cys are synthesized Phe and Met, respectively.

# Synthesis from α-keto acids



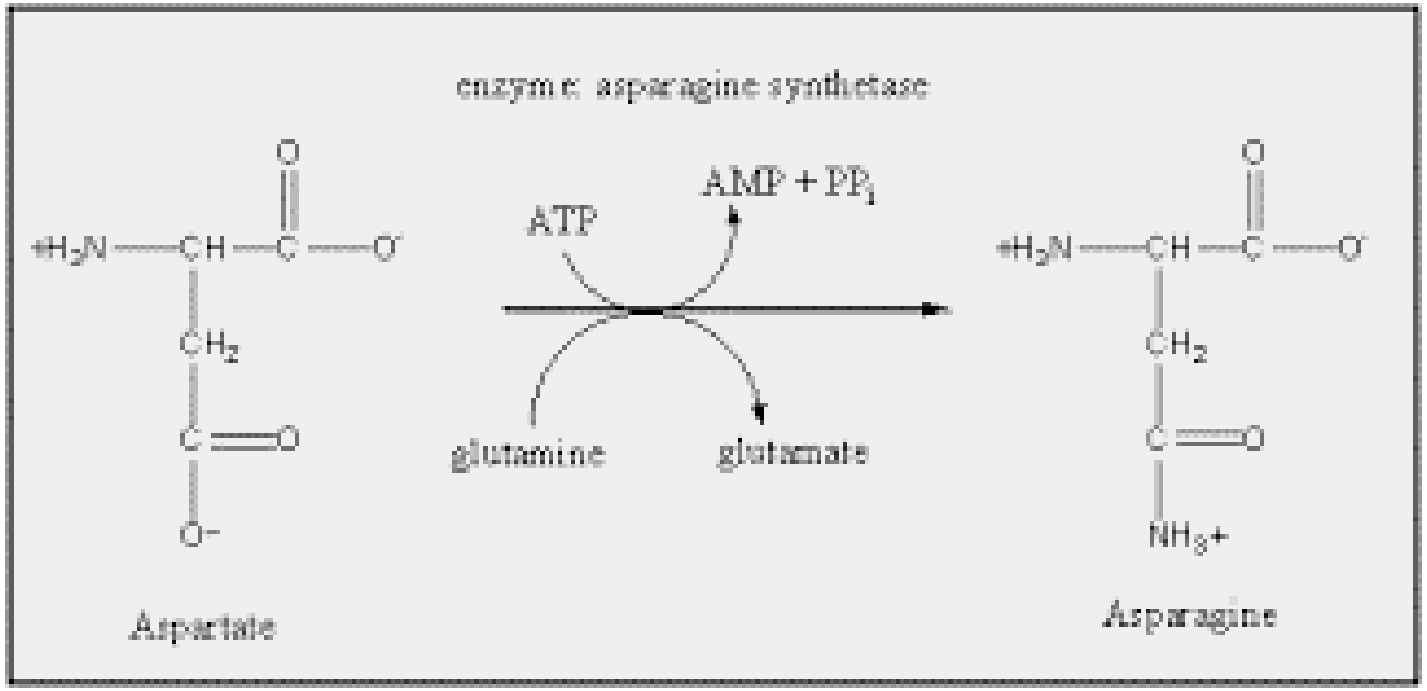

Ala, Asp, and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively.

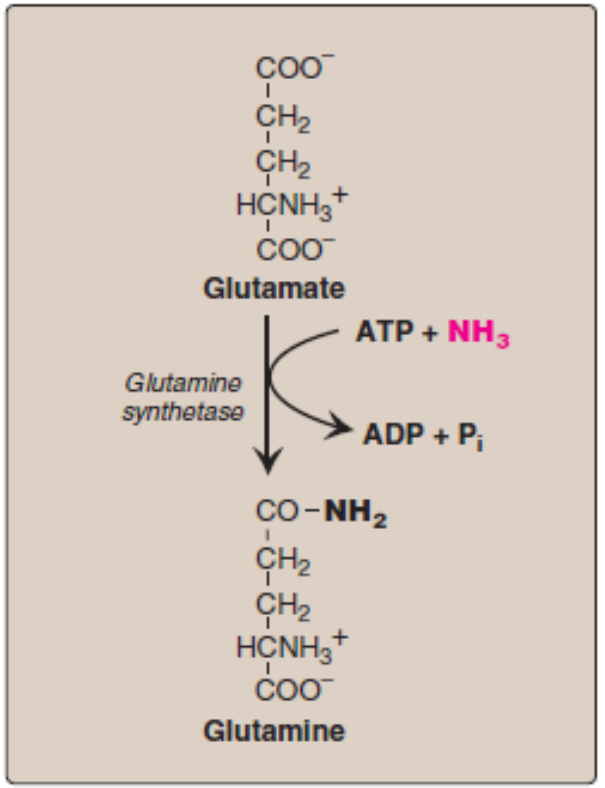
Glu can also be synthesized by the reverse of oxidative deamination, catalyzed by glutamate dehydrogenase

# Synthesis by amidation

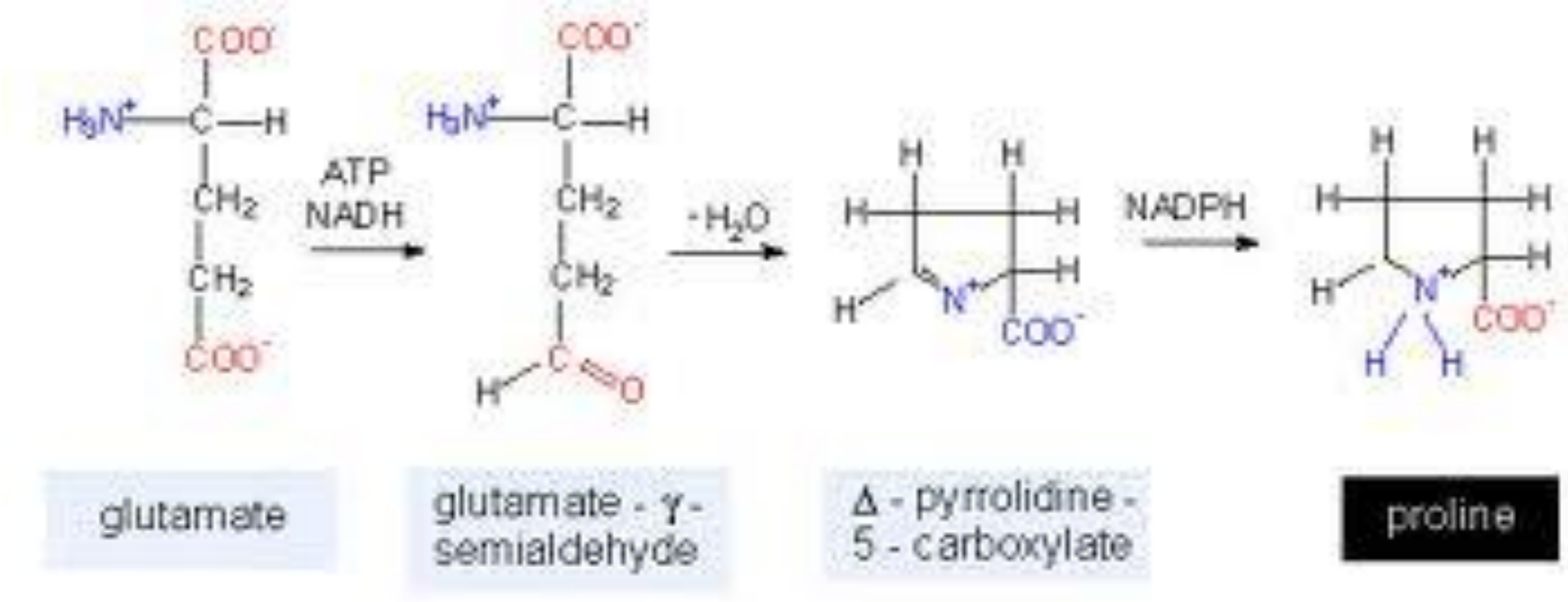
**1. Gln** is formed from Glu by glutamine synthetase

**2. Asn** is formed from Asp by asparagine synthetase, using glutamine as the amide donor.



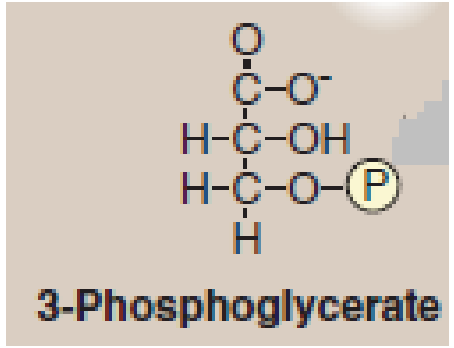
# Proline




Glutamate is converted to proline by cyclization and reduction

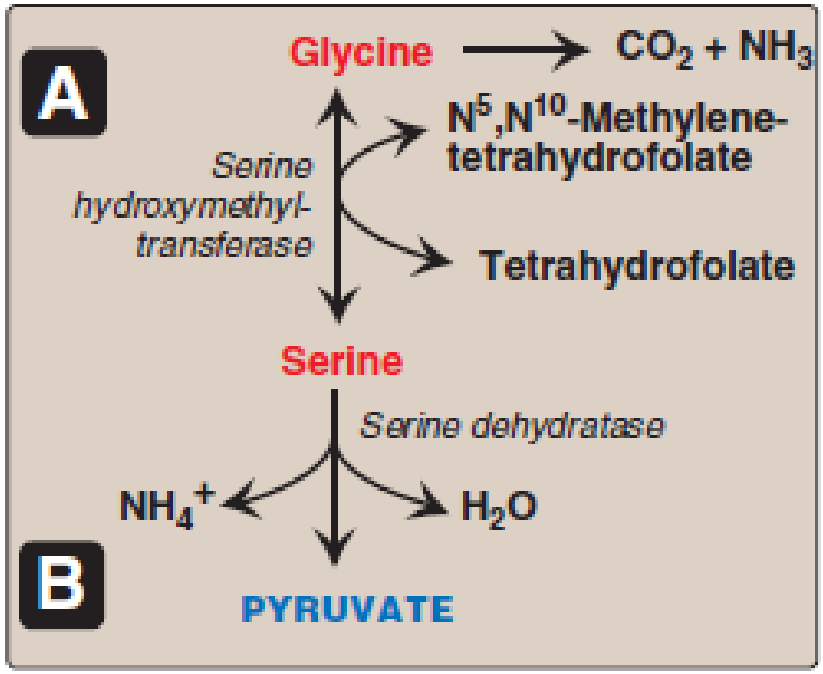
# Serine, and glycine

1. **Ser** arises from 3-phosphoglycerate that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phospho serine. Serine is formed by hydrolysis of the phosphate ester.




- Ser can also be formed from glycine through transfer of a hydroxymethyl group by serine hydroxymethyl transferase

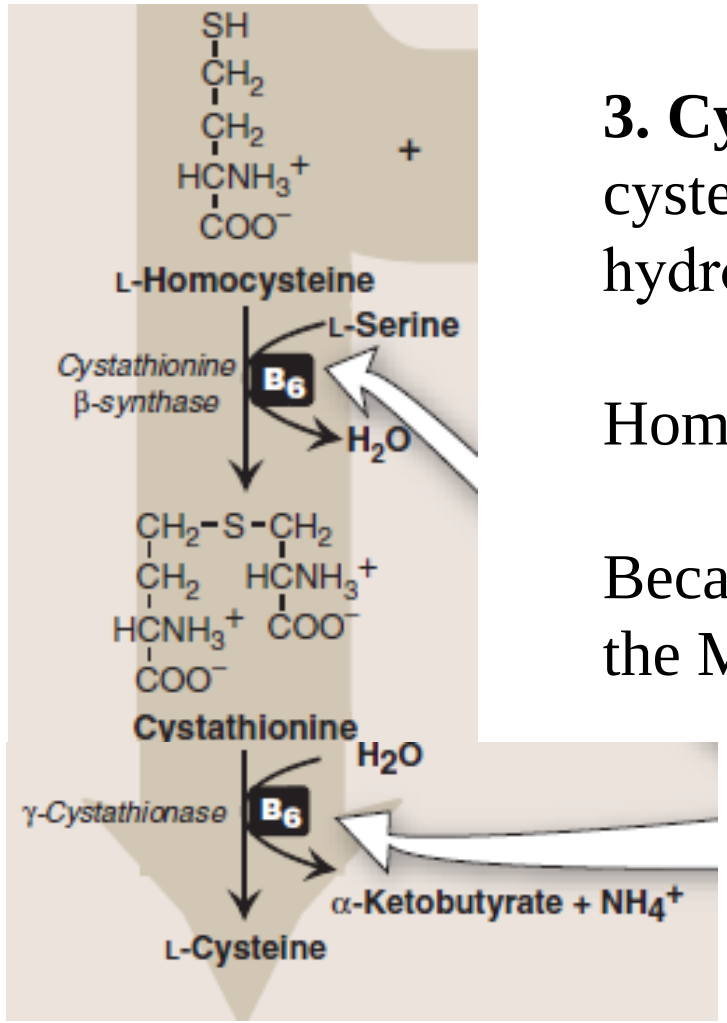
- $N^5$,$N^{10}$-methylene- THF is the one carbon donor




**2. Gly** is synthesized from serine by removal of a hydroxymethyl group, also by serine hydroxymethyl transferase

- THF is the one carbon acceptor.

# Cysteine




**3. Cys** is synthesized by two consecutive reactions in which homo cysteine combines with serine, forming cystathionine that is hydrolyzed to α-ketobutyrate and Cys

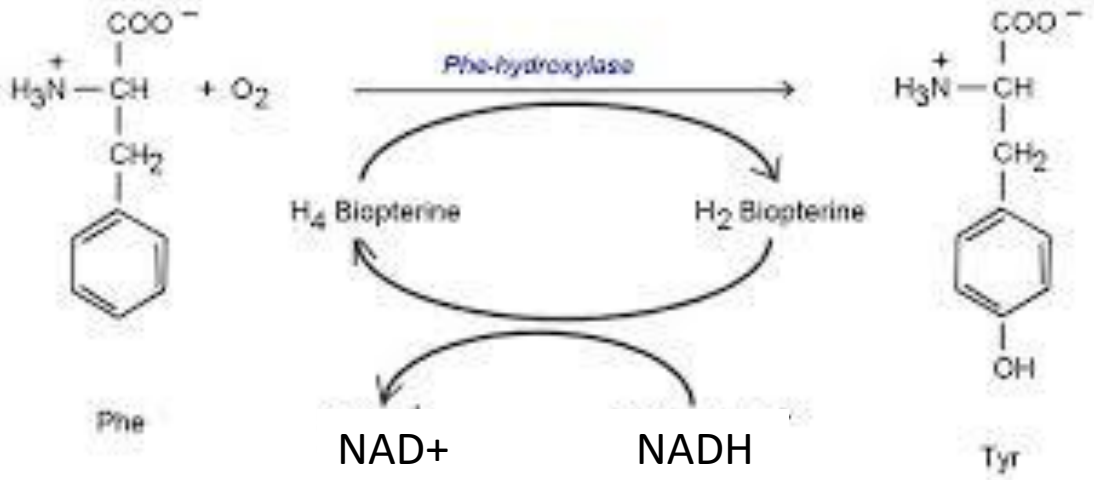
Homocysteine is derived from Met

Because Met is an essential amino acid, Cys can be synthesized the Met dietary intake is adequate.

# Tyrosine

Tyr (non essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase.

The reaction requires molecular oxygen and the coenzyme tetra hydrobiopterin (BH4)

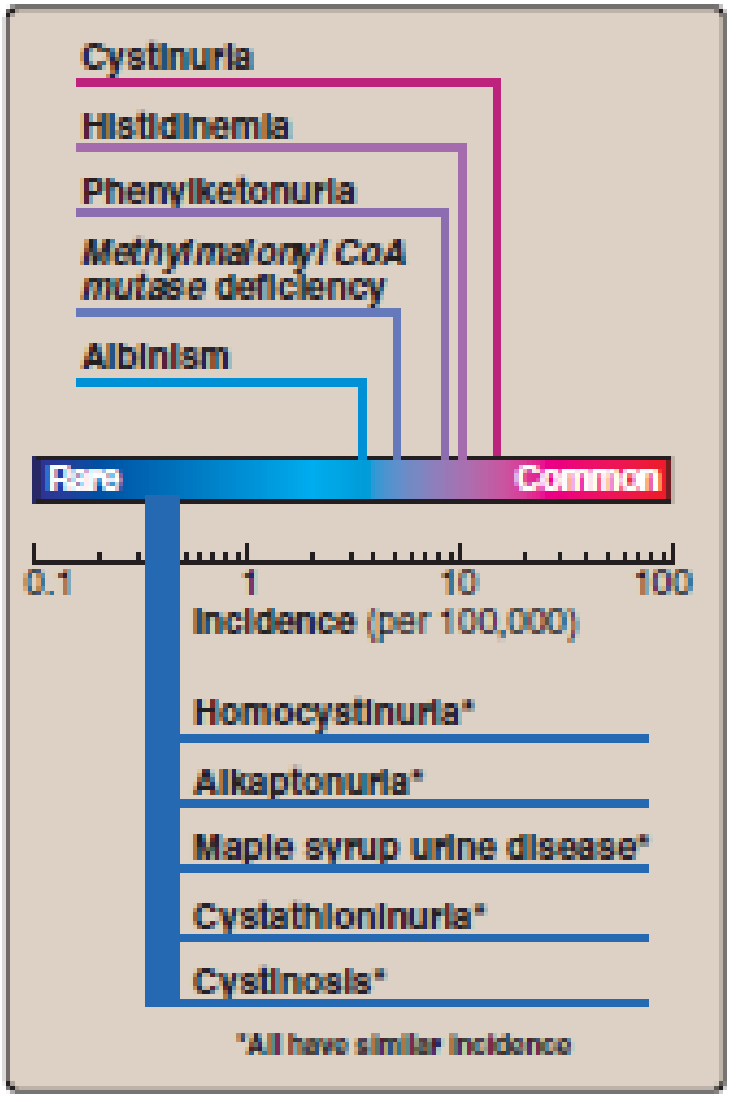



BH4 is oxidized to dihydrobiopterin (BH2).

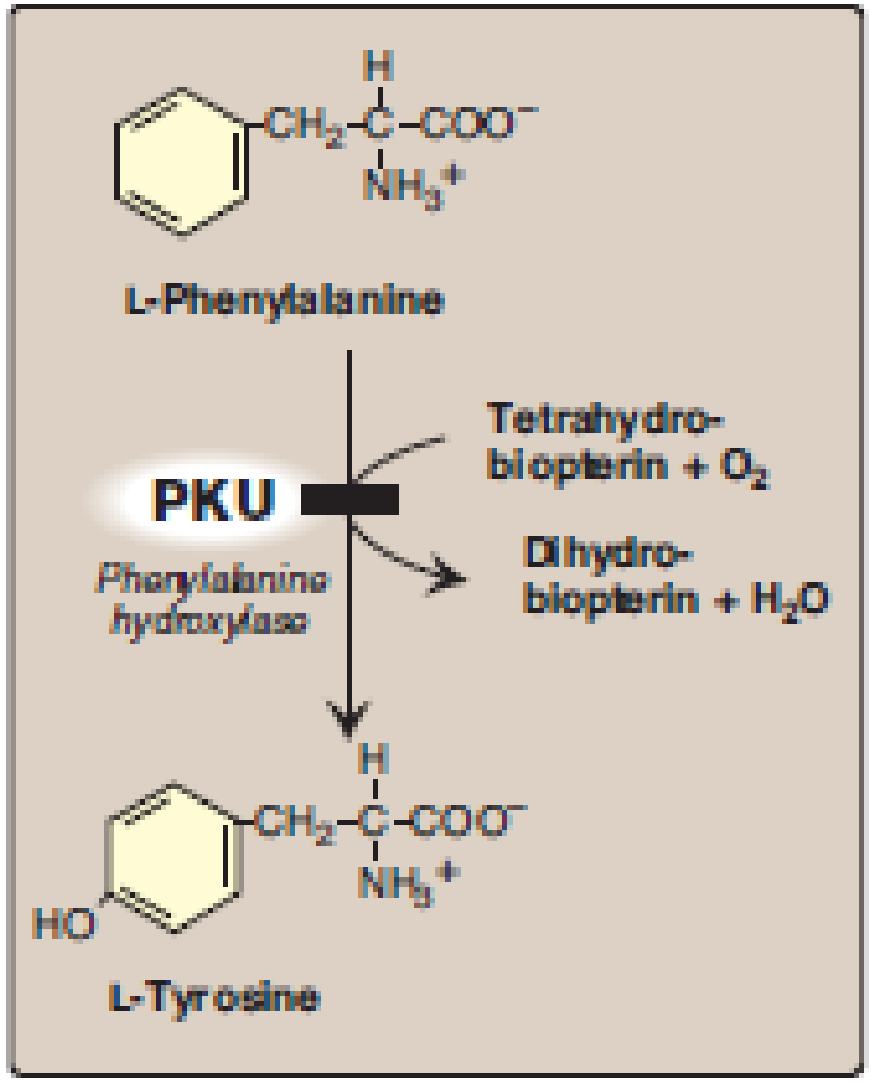
BH4 is regenerated from BH2 by NADH-requiring dihydropteridine reductase.

# Metabolic defects in amino acid metabolism

The inherited defects of AA metabolism if stay untreated result in mental retardation or other developmental abnormalities because of the harmful accumulation of metabolites.



# Metabolic disorders: Phenylketonuria (PKU)




The most common inborn error of amino acid metabolism (prevalence 1:15,000).

Due to phenylalanine hydroxylase deficiency

Biochemical changes: accumulation of phenylalanine (and a deficiency of tyrosine)

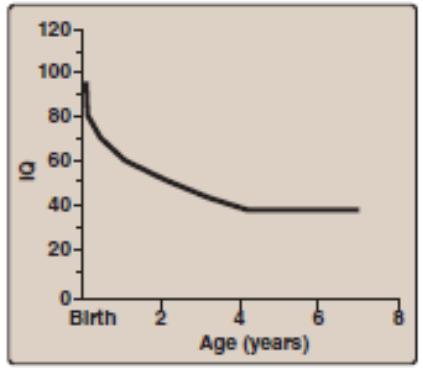
Tyr cannot be synthesized from Phe and becomes an essential amino acid.

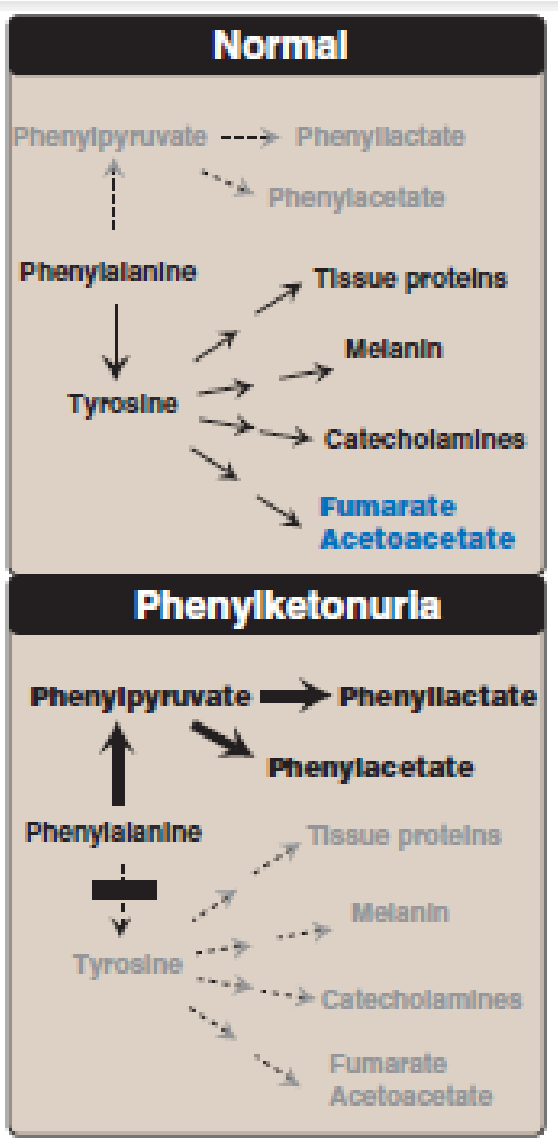
Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).

# Characteristics of classic PKU:

- **Elevated phenylalanine** in tissues, plasma, and urine.
- **The characteristic musty "mousey" urine odor** due to phenyllactate, phenylacetate, and phenylpyruvate
- **CNS symptoms:** Mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow
- **Hypopigmentation:** fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.

Neonatal screening programs



# Neonatal screening and diagnosis of PKU

PKU is treatable by dietary restriction.

Lack of neonatal symptoms

At birth, infants with PKU have normal blood levels of Phe because the mother clears the extra Phe through placenta

Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Treatment:
Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals)

Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation)

Aspartame should be avoided since it contains Phe.

# Maternal PKU

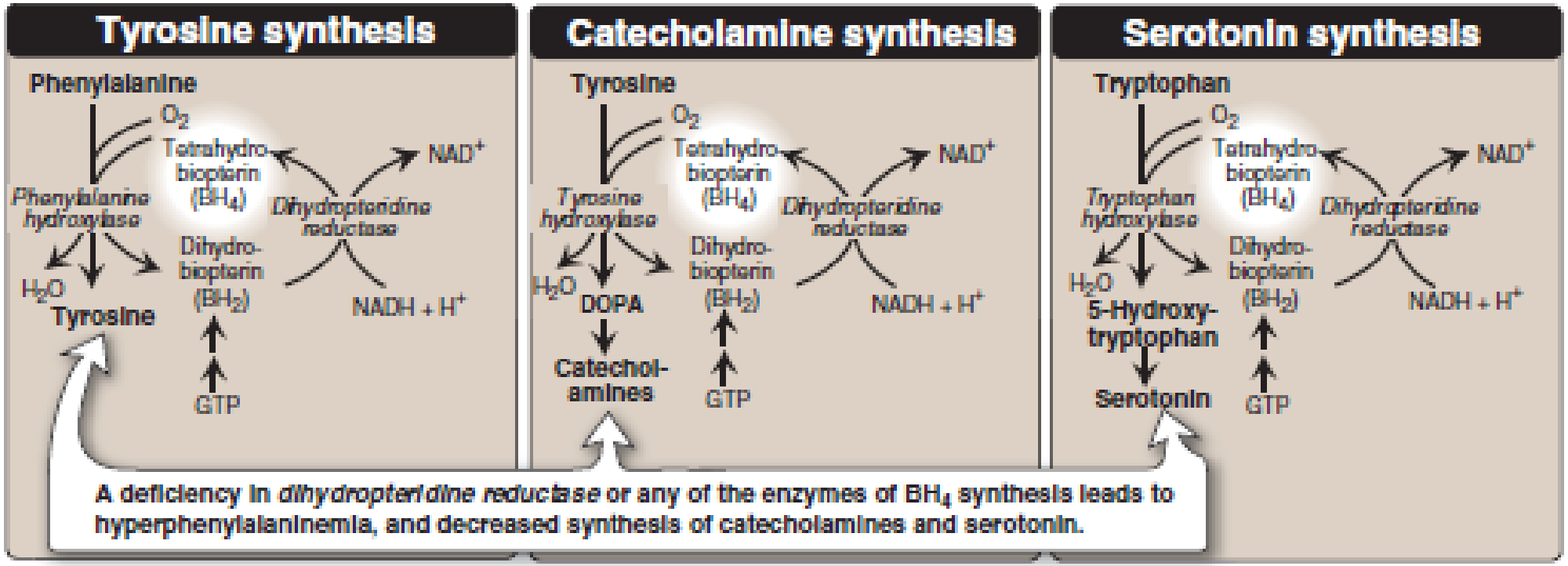
- High blood Phe levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus

- Phenlyalanine is a teratogen (an agent or factor which causes malformation of an embryo).

- Dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.


https://www.npkua.org/Portals/0/PDFs/2018Conference/Breakouts/Maternal%20PKU%20NPKUA%202018%20hobbs%20RS%20FINAL.pdf?ver=2018-08-08-171024-600

# Metabolic disorders: Hyperphenylalaninemia




Dihydropteridine reductase deficiency:

Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters.

Replacement therapy with BH4 or L-DOPA and 5-hydroxytryptophan (products of the affected tyrosine hydroxylase–and tryptophan hydroxylase–catalyzed reactions) improves the clinical outcome

# Albinism

A group of conditions in which a defect in Tyr metabolism results in a deficiency in the production of melanin.

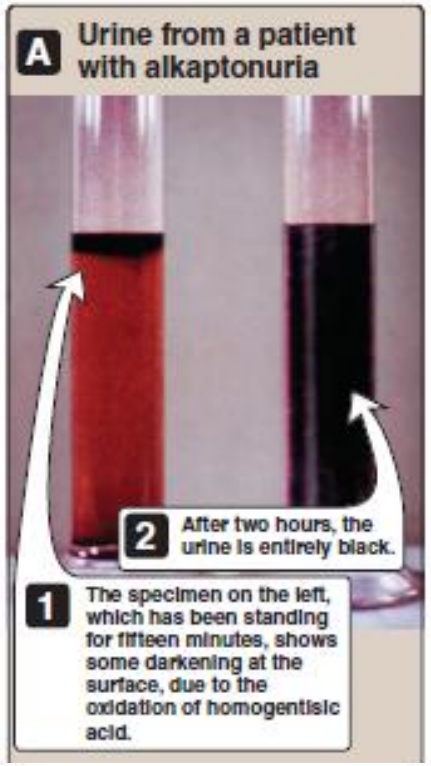
Partial or full absence of pigment from the skin, hair, and eyes.

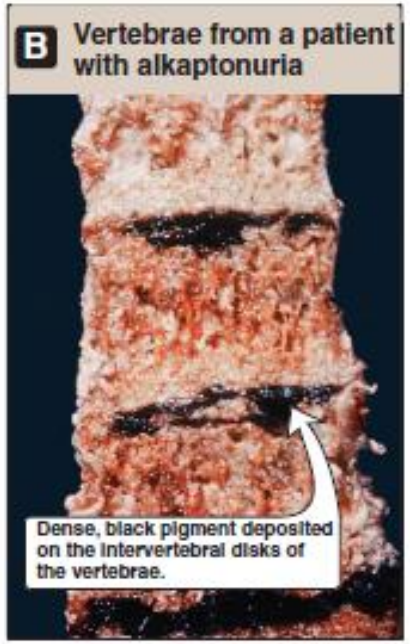
Inheritance modes:
AR (primary mode), AD, or X-linked.

Complete albinism (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase

Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

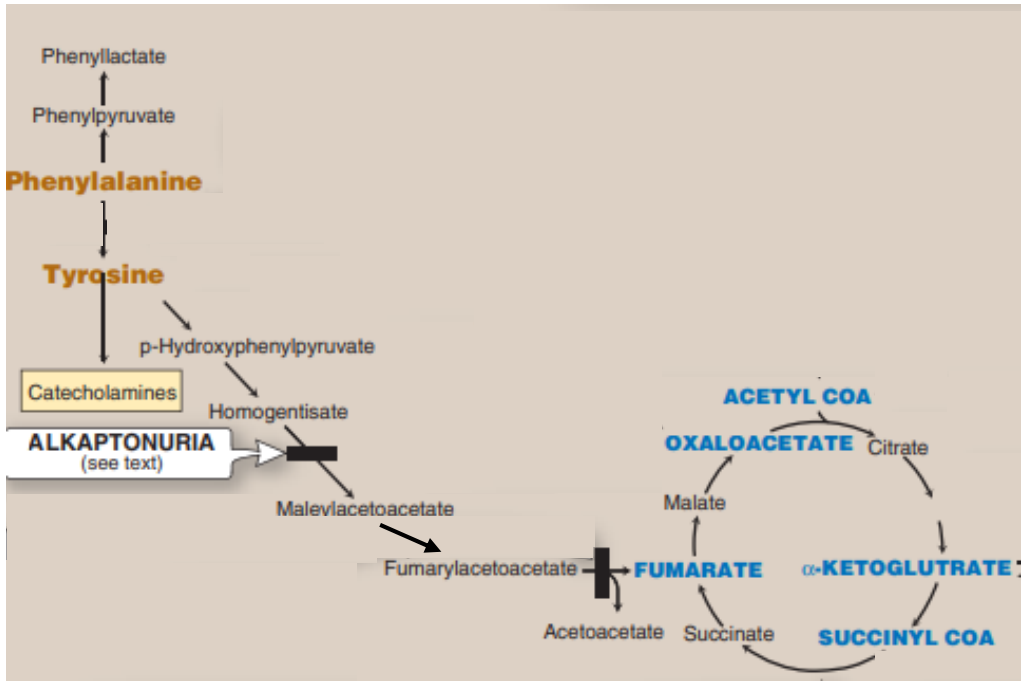
# Alkaptonuria (Alcaptonuria)




A rare metabolic condition, however, cases were found in Jordan

A deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr)




Characteristic symptoms: Not life threatening

Patients are usually asymptomatic until age 40.

-Homogentisic aciduria

-Large joint arthritis

-Black ochronotic pigmentation of cartilage and collagenous tissue

-Dark staining of the diapers can indicate the disease in infants

Treatment: diets low in protein—especially in Phe and Tyr reduce homogentisic acid levels, and the pigment deposited in body tissues.

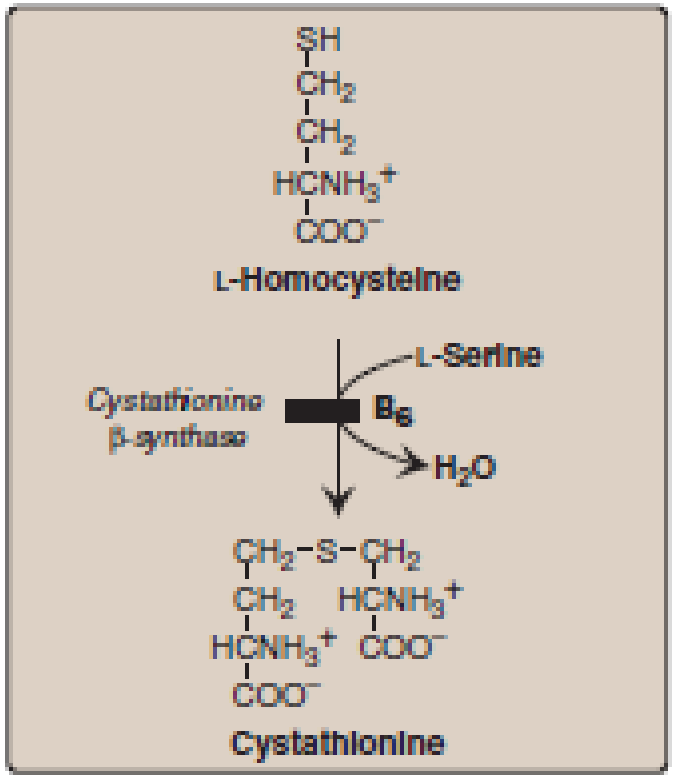
# Homocystinuria

Defects in the metabolism of homocysteine.

Mode of inheritance: AR

High plasma and urinary levels of homocysteine and Met and low levels of Cys.

The most common cause is a defect in cystathionine β-synthase that converts homocysteine to cystathionine



# Maple syrup urine disease (MSUD)

Rare (1:185,000), autosomal recessive (AR) disorder, most cases are heterozygotes

Partial or complete deficiency in branched-chain α-keto acid dehydrogenase complex that decarboxylates Leu, Ile, and Val

Branched-chain amino acids are an important energy source in times of metabolic need

Accumulation in the blood causes a toxic effect that interferes with brain functions.

Signs and symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.

If untreated, MSUD leads to mental retardation, physical disabilities, and even death.
**Screening and diagnosis:** prenatal diagnosis and neonatal screening are available.

**Treatment:** a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels.

Early diagnosis and lifelong dietary treatment is essential for child normal development.

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